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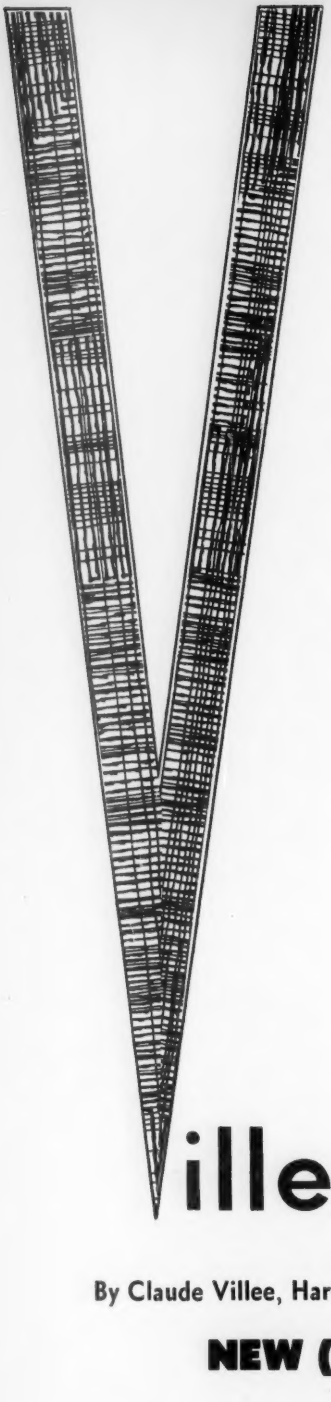

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Radiation and Health

Companion bills introduced in the Senate (S. 1228 by Senator Neuberger and several colleagues) and in the House (H.R. 4820 by Representative Porter) propose the establishment of a National Radiation Health Institute in the Public Health Service. The institute would be empowered to conduct research, support training, initiate control programs, make grants-in-aid for research, and be responsible for the study and treatment of diseases arising from atomic radiation.

It may be questioned whether the establishment of a new institute in this field is desirable. The Atomic Energy Commission is already carrying out many studies on the effects of radiation on health and is working in close cooperation with the Bureau of State Services of the Public Health Service to measure radiation and to determine the accumulation of radioactivity in water, soils, and foods. The enabling act of the Public Health Service is broad enough to permit the bureau to expand these activities and to put into effect any necessary public health controls.

But, if the proposed institute duplicates services already provided, it does not face up to the larger issues, for the bills would apparently confine the institute to the study of diseases and conditions arising from *atomic* radiation. At present, atomic radiation, in the usual sense, accounts for only a small fraction of the total radiation to which we are exposed: the background radiation and the average exposure to x-rays account for most of the radiation burden. So far as health is concerned, the source of radiation makes little difference. One roentgen is about as bad as another. Consequently, any radiation health agency should deal with radiation from all sources. The problem merits a comprehensive, not a piecemeal, solution.

The bills also propose that another agency, the Office of Radiation Health Control, be established in the Public Health Service. This office would in effect be empowered to carry out the recommendations made in the National Academy of Sciences' report on *The Biological Effects of Radiation* by "making available to each person in the United States a voluntary, simple and efficient means of keeping a permanent record of measurable amounts of radiation to which he is exposed during his lifetime." Would the considerable effort required to keep such records for a large part of the population be worth while? Possibly the only sound way to find out would be to try one or more pilot programs. Such records would obviously be of value to anyone who decided to work in an atomic installation. For others, the value is at least debatable, for, at the risk of oversimplification, it may be said that the decision to expose anyone to x-rays is governed primarily by the necessity for diagnosis and treatment, not by the record of previous exposure.

The relation of radiation to health is a problem of vast complexity. Much has to be learned before we will be able to plan an effective program. Perhaps the best course to follow would be to let existing agencies gain more experience before deciding that it is necessary to establish new ones.
—G. DUS.

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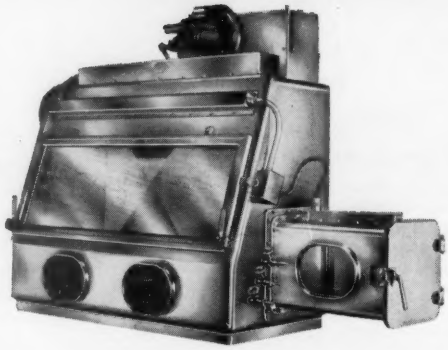

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Chemistry of the Brain

Past Imperfect, Present Indicative, and—Future Perfect?

Irvine H. Page

Only 30 years ago a prominent neurologist, while discussing with me the future of neurochemistry, referred to it as the chemistry of "brain hash." For him, neurochemistry had no more attractiveness than the chemistry of any other hash. As far as he knew, the brain had no organized chemical mechanisms; it consumed no oxygen and evolved no carbon dioxide, or did these things only incidentally. His mind was concerned wholly with tracts and lesions. Yet this was at a time when the chemical relationships of other organs were well established. But the nervous system was maintained in splendid isolation, almost as though there were unconscious fears that the rude attack of scientists carried with it the seeds of self-destruction. And we shall see that there may be some truth in this premonition.

J. L. W. Thudichum many years ago initiated work on neurochemistry, oddly enough at the instigation of his government, to determine the effects of typhus on the brain. His was an amazing career of scientific productivity that I have described in my first book on the *Chemistry of the Brain* (*1*). Thudichum thought well of his work, for he said, "In order, however, that the reader may not, from this avowal, come to any erroneous conclusions regarding my own estimate of the value of my researches communicated in this treatise, I undertake to assure him that they are of fundamental importance, and that all further developments in chemical neurology must start from them as a basis." And, in a way, Thudichum was right.

But the flame died; clinical neurology and Freudian psychiatry took over and nothing was heard of either Thudichum or neurochemistry until the 1920's, when workers in this country began to prove that nerve tissue had indeed a metabolism. The necessity to prove this seems naive and strange in retrospect, but people were greatly imbued with the implications of the analogy between transmission of an electric current over a copper wire and transmission over nerves.

By 1923 Kraepellin had expressed the wish to have a department of brain chemistry in the projected Kaiser Wilhelm Institute for Psychiatry in Munich, and in 1928 I had the fun of implementing the concept. This was, I believe, the first modern laboratory devoted wholly to the chemistry of the brain. There were, of course, many other laboratories in which various projects concerned with nerve tissues had been investigated. In England, Quastel was beginning his fine work. But somehow, our efforts failed to fire the imaginations of either investigators or clinicians until around the early 1940's, when Gerard, Elliott, Himwich, von Euler, McIlvain, and their like appeared, along with some strong encouragement from other fields of endeavor. The anticonvulsants, chemical transmitters of nerve impulses, tranquillizers, lysergic acid diethylamide, and serotonin all contributed to the red glow of incipient intellectual combustion. The chemical mechanisms of the brain were no longer to be denied; the era of the subjective was being crowded and complemented but not replaced by an era of the objective. The movement was long overdue and illustrates how a method such as psychoanalysis, for example, no matter how worthy in itself, if followed to the exclusion of other investigative facets, seriously hampers development of a discipline.

What I have to say is merely illustrative of the "past imperfect, present indicative, and—future perfect?" My purpose is to examine a field of endeavor that is not yet fully formed in the hope that adumbrating its lines of growth may facilitate and better its development.

Control of Arterial Pressure as a Neurochemical Function

Many of the functions of the body that are maintained homeostatically are in part, but seldom wholly, under the control of the nervous system. Normal arterial blood pressure is a good example. The vasomotor centers in the medulla seem to control it almost completely under ordinary circumstances. This does not mean, however, that these centers alone control blood pressure and cardiovascular reactivity—that is, the degree to which the cardiovascular system responds to vasoactive drugs.

In Fig. 1 I have oversimplified the problem for the sake of stressing the principle involved. Note that the vasomotor centers are subjected to a variety of controlling mechanisms, most of which may be chemical. Psychic functions may have a profound effect on these centers, but the mechanisms by which they act is quite unknown. There is a certain "guilt by association" in the effects on blood pressure of the disease called acute porphyria. I remember very vividly a patient we studied who had this disease, especially because for more than a year we misdiagnosed her disease as essential hypertension with conversion hysteria. She was an example of a neurotic girl at her worst, and that can be pretty bad. But she had sufficient hypertension to keep our interest. Things went from bad to worse in the hospital until finally, after bouts of convulsions, temper tantrums, and altogether bizarre behavior, she was dismissed. The correct diagnosis was made by chance in another

Dr. Page is director of research at the Cleveland Clinic Foundation and professor of experimental medicine of the Frank E. Bunts Educational Institute, Cleveland, Ohio. This article is based on his vice-presidential address to Section N–Medical Sciences, during the New York meeting of the AAAS, 26–30 Dec. 1956.

hospital, so often referred to sneeringly as "elsewhere." I say by chance because a sample of urine was allowed to stand for hours before it was sent to the laboratory, and during this period of inefficiency it turned deep red. When the porphyria spontaneously cleared, possibly because no more barbiturates were given, the girl almost miraculously became a thoroughly well-adjusted and nice person; her hypertension disappeared. Was her case an effect of the upset porphyrin metabolism on the psychic functions of the brain? Or was it an effect directly on the brain itself and on the autonomic system which affected both her behavior and her arterial pressure? Possibly hypertension is the result of direct action of porphyrins on the smooth muscle of blood vessels. I do not know the answer, but the problem is an interesting one and suggests that Klüver's finding (*2*) of porphyrins in the central nervous system needs much more penetrating study.

It is believed that the vasoconstrictor centers are to some degree influenced by the access to them of humoral agents such as adrenaline and acetylcholine, drugs having a "central action." Curiously, these drugs often seem to have quite the reverse effect than they do when they are injected peripherally: adrenaline causes a fall in arterial pressure when it is injected into the cerebral circulation, and acetylcholine causes a rise. I have no idea how important this mechanism is in the control of normal blood pressure.

Another aspect of the problem of the interrelationships of blood-borne substances and neurochemical reactions is the chemical environment of the vasomotor centers. The chemical environment to a considerable degree determines the intensity of the responses of the centers. The *p*H and carbon dioxide concentration are among the better recognized environmental factors, but there must be many, many others which not only provide for the well-being of the brain tissues but also determine their ability to respond.

Perhaps the most important neurochemical control of blood pressure is mediated by the buffer reflexes. These reflexes, in turn, seem to be initiated either by distention of the arterial wall (baroceptors) or by the chemical composition of the blood (chemoceptors). The distention of the arterial wall is in itself determined not only by the height of the blood pressure and the character of the pulse wave but by a variety of chemical agents that affect distensibility. I shall not pursue the matter further, lest I inadvertently stray back into the fields of arteriosclerosis and hypertension, from which I make my living. But let me press the point that the control of these vital functions of the body, blood pressure and tissue perfusion, is, in the final analysis, largely neurochemical.

Neurosecretion

The secretory function of the brain is in one way well known and in another way almost unknown. Most scientists are familiar with the fact that adrenaline and noradrenaline are secreted by nerve tissue and that the hypothalamic-pituitary system secretes and stores hormones. But there the thinking stops, and any suggestion that the brain has as one of its functions secretion of hormonelike materials is usually met with broad skepticism. Let us look at some of the evidence that supports the suggestion of neurosecretory action.

Hormones, including molt-inhibiting, metabolic, and chromatophorotropic hormones, are present in parts of the central nervous system of crustaceans (for review, see B. Sharrer, *3*, *4*). Some of these hormones are secreted by the neurosecretory cells of the x-organ and transported through the axons of the cells to the sinus gland for storage.

Neurosecretion was first demonstrated in the nucleus preopticus in teleostome fish and subsequently has been found also in reptiles, birds, and mammals. The secreted material from the hypothalamus is transported to the neurohypophysis via the axons of the neurosecretory cells that terminate in the pituitary stalk and in the pars nervosa. The endings in mammals often appear as bulbous swellings known as Herring bodies.

The work of the Sharrers (*3*) has largely established the concept that, both in vertebrates and invertebrates, neurosecretory cells have the dual role of neurons and glands. In vertebrates, however, the secure evidence is so far limited to the neurosecretory cells in the hypothalamus and their relationship to the pars nervosa; the hypothalamus appears to secrete vasopressin and the pars nervosa to store it.

One of the more fascinating observations is that severance of the autonomic recurrent nerve in the insect, *Leucophaea,* results in development of tumors in the organs innervated by this nerve, notably the anterior portion of the gastrointestinal canal (Sharrer, *4*). Stomach tumors account for the majority of deaths following nerve section. The evidence is clearly in favor of the theory that the nervous system can act as a secretory system having important effects on the body.

Another example of a substance released by secretory activity may be "cerebrotonin." We think we have shown that cerebrotonin is released from the brain when the central end of the cut vagus-sympathetic trunk is stimulated electrically (Taylor and Page, *5*). This vasopressor material seems to be different from all known hormones. It has not yet been identified, nor has its site of release been determined. If this substance is physiologically active, and is not vasopressin, it would provide yet another method for the control of vasomotor tone by the brain. Although we have no evidence to suggest that it does so, it is the sort of substance that could help, in part, to maintain blood pressure at relatively normal levels after section of the spinal cord and vagus nerves.

But these are only examples of the important possibility that the nervous system does more than exert control by means of transmitted nervous impulses; it can also regulate directly through chemical secretion produced by nerve cells. This aspect of neurochemistry has received little attention.

Autonomic Representation

It is odd that so far we have learned a good deal more about the chemical events in the autonomic nervous system than we have about events in other parts of the nervous system. We are not at all sure, for example, why transmission within the brain seems less easily blocked by atropine or hexamethonium than transmission across autonomic ganglia. Let me give just a few examples of what I mean.

Largely through the work of Ulf von

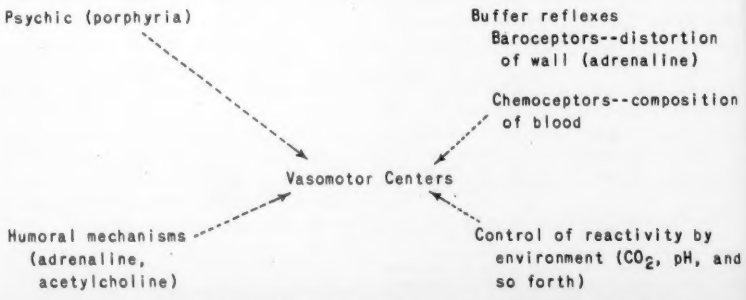

Fig. 1. Control of arterial blood pressure as a neurochemical problem.

Euler, it has been shown that noradrenaline is liberated at adrenergic nerve endings and that adrenaline is liberated as well, in some cases. Recently Peter Holtz (*6*) has shown that a decarboxylase exists in nervous tissue which decarboxylates 3,4-dihydroxyphenylalanine to hydroxytyramine, thus providing the building material, or precursor, for synthesis of noradrenaline within the nervous system itself. But note that it is present in highest concentration in postganglionic sympathetic nerves and that almost none is present in cortex.

Vogt (*7*) found high concentrations of sympathin in the hypothalamus and the area postrema, less in the midbrain, and still less in the medulla and medial thalamus. It was found nowhere else. Clearly, the sympathin content was associated with the central representation of sympathetic activity. In cats, 7 percent, and in dogs, about 14 percent of the sympathin is adrenaline and the remainder noradrenaline. Vogt's suggestion is that sympathin is the adrenergic activator of secretion by the anterior pituitary, chiefly because drugs that stimulate these centers reduce the content of sympathin.

The content of substance P, a smooth muscle stimulator of polypeptide structure discovered by von Euler and Gaddum (*8*) and extensively studied by Pernow (*9*) parallels the content of acetylcholine except in the hypothalamus, which shows the highest concentration of substance P. According to MacIntosh (*10*), still another substance, acetylcholine, is found in highest concentration in the basal ganglia and midbrain of cats.

Serotonin is also found in the brain in relatively high concentration. It has, like so many other substances, been suggested as a transmitter. Its distribution in brain is not unlike that of noradrenaline (Amin, Crawford, and Gaddum, *11*) and may therefore be associated with central autonomic representation. But Twarog (*12*) suggests that serotonin has a specific inhibitory action to acetylcholine in *Mytilus* muscle. Marrazzi and Hart (*13*) found serotonin 6 to 8 times as potent as lysergic acid diethylamide and 30 times as potent as adrenaline in ability to inhibit cerebral synaptic transmission. As a neurohumoral inhibitor, serotonin might be very effective.

Histamine is found principally in postsynaptic sympathetic fibers, according to von Euler (*14*). In the brain, its concentration is high only in the cerebellum and hypothalamus. Histaminergic synapses have not been demonstrated so far.

The hypothalamus thus seems to be the "*Beilstein*" of the brain, containing, as it does, the highest concentrations of noradrenaline, serotonin, substance P, and histamine; it contains acetylcholine, adenosine triphosphate, and vasopressin as well.

There seems to be among the physiologically active substances a certain economy of function such that a relatively few substances have a great variety of actions. The catechol amines, widespread throughout the body, not only mediate sympathetic transmission and affect importantly the carbohydrate metabolism but, in addition, they, or their degradation products, seem to affect psychic function. Serotonin and other indole derivatives seem likewise to exert multifaceted actions, and less could not be said for histamine and, possibly, substance P. It is this multiplicity of action combined with the economy of molecular species that makes the semi-isolated brain a chemical kingdom largely sufficient to itself.

In connection with autonomic representation, I want to mention again the problem of inhibition of transmission within the brain, for many of these substances have this property. Marrazzi and Hart (*13*) first pointed out that a variety of adrenergic substances inhibit synaptic transmission. Later they found serotonin to be the most powerful inhibitor of all the substances tested. From this they suggest that some forms of mental disturbance result from an imbalance between serotonergic and adrenergic inhibition and cholinergic excitation in the more susceptible cerebral synapses. Inhibition of the transcallosal potential was found by Slocombe, Hoagland, and Tozian (*15*) to parallel diminishing spontaneous electric potentials resulting from serotonin in rat's brain. The effectiveness of the inhibition under Pentothal anesthesia was in the following order: serotonin, lysergic acid diethylamide, adrenaline, noradrenaline, and last, adrenochrome. Slocombe, Hoagland, and Tozian suggest that these drugs have a common mode of action. Quite recently Bazemore, Elliott, and Florey (*16*) have isolated what appears to be Florey's factor I, which is believed to be a transmitter substance of inhibitory neurones. Interference with its action may be the basis of the convulsive effects of some drugs. At least part of the action of factor I seems to be due to γ-aminobutyric acid. This acid had previously been found in brain; it is produced by the action of a decarboxylase on glutamic acid.

Psychotomimetic Drugs

Drugs that produce mental disturbances have been known since the dawn of history, but it is only recently that they are being studied from the point of view of their actions in terms of chemical mechanism. Former observers, of whom there were many astute ones, were content to record the effects of the drugs but showed no concern for their chemical pharmacology.

There is no need here to review the subject. Instead I shall select lysergic acid diethylamide as a prototype, because of its ability, even in minute quantities, to produce mental change, and because suggestions have been made to explain how it acts.

In a way, this story began with the isolation and determination of the structure of lysergic acid by Walter Jacobs and Lyman Craig in 1936. I was working at the Rockefeller Institute for Medical Research when this was done and remember being told about the project by Craig as we were going onto the tennis court one day, which proves the value of tennis courts over convention halls as a means of communication. A. Stoll and A. Hofmann in 1938 synthesized *d*-lysergic acid diethylamide, but it was not until 5 years later that Hofmann noted (*17*) on Friday, 16 April 1943, that, "I was forced to stop my laboratory work in the middle of the afternoon and to go home, as I was overcome by a peculiar restlessness associated with mild dizziness. Having reached home, I lay down and sank into a kind of delirium which was not unpleasant and which was characterized by extreme activity of the imagination." Hofmann had accidentally ingested some lysergic acid diethylamide. He was scientist enough to suspect, and later prove, the relationship between the substance he was working with and the hallucinations. In 1947 W. A. Stoll (*18*) reported a careful, psychiatrically oriented study and so began the story of a drug that is having a profound effect on modern psychiatric thinking.

The amount of some substances required to affect thought is so minute that concern with quantum effects is suggested. A substance like lysergic acid diethylamide elicits profound psychobiological actions, according to Axelrod, Brady, Witkop, and Evarts (*19*), when concentrations of the order of 0.0003 micrograms per gram of brain tissue are administered; the necessary concentration is probably lower than this since the substance is rapidly metabolized (Stoll, Rothlin, Rutschmann, and Schalch, *20*). In the mouse the half-life is only 7 minutes. If quantum effects are, in fact, involved, it follows that understanding itself will be subject to the same indeterminacy proposed by Heisenberg for quantum mechanics.

Another part of the story begins with the discovery of serotonin (5-hydroxytryptamine) in 1947 and the demonstration, both in this country and in England, that it is present in very considerable amount in brain tissue. Wooley and Shaw (*21*) subsequently synthesized a number of competitive antagonists to

serotonin and, on the basis of the actions of the antagonists and of the harmala alkaloids, made the shrewd suggestion that serotonin might be concerned in mental disease.

In 1954 Gaddum (*22*) showed that lysergic acid diethylamide is a powerful antagonist of serotonin's action on the uterine strip and also suggested that the concentration of serotonin in the brain had much to do with maintaining normal mental functions. Serotonin might thus be an antagonist for hallucinations caused by lysergic acid diethylamide. Actually, administered serotonin does not appear to cross the blood-brain barrier, hence could not be expected to be effective. Even so, there is evidence that it is not a simple antagonism, for Rinaldi and Himwich (*23*) have shown that azacyclonol, α-(4-piperidyl-benzhydrol) abolishes the electroencephalographic changes produced by lysergic acid diethylamide in rabbits. Further, more recent work has shown that azacyclonol is effective in patients that have been given lysergic acid diethylamide and in eliminating the hallucinatory phenomena during acute schizophrenia (Fabing, *24*). Clearly the actions of lysergic acid diethylamide on mental phenomena are many sided and highly complex. Nonetheless, the intellectual ice has been broken and the problems of neurochemistry are taking form. This is the beginning of progress in research.

There followed a series of important papers by Brodie and Udenfriend in which it was shown quite conclusively that reserpine causes the release of the bound serotonin in brain, enabling it to be destroyed later by amine oxidase. Serotonin is believed by Brodie and Udenfriend to be the intermediary for the tranquilizing action of reserpine.

Reserpine has a prolonged action, yet actually disappears from both plasma and brain shortly after its intravenous administration. According to Hess, Shorr, and Brodie (*25*), it achieves a maximum level in the brain in about 15 minutes. Its effects are related temporally to change in serotonin, and they seem to be a consequence of this change. The primary action of reserpine is suggested by them to be impairment of the capacity of cells to bind serotonin. The free serotonin, even though it is low in concentration, is presumed to exert sedative and other effects that persist until the cells regain their capacity to bind serotonin.

Serotonin itself does not appear to cross the blood-brain barrier and it is not known whether the serotonin within the brain is exogenous or endogenous, or both. Udenfriend, Bogdanski, and Weisback (*26*) have partially solved this problem in a very ingenious way. As they showed earlier, 5-hydroxytryptophan is converted to serotonin by a specific decarboxylase that is found in many mammalian tissues. Administration of this amino acid resulted in the appearance of serotonin in such organs as liver, kidney, heart, and uterus, which normally contain none. Since 5-hydroxytryptophan penetrates the blood-brain barrier, a marked increase in brain serotonin occurs. In animals, it was possible to raise cerebral serotonin 20-fold. Of great interest is their observation that the effects at these high levels resemble those seen after administration of lysergic acid diethylamide.

J. L. W. Thudichum, founder of neurochemistry.

Just as in all research problems, difficulties have recently arisen that throw doubt into this boiling scientific cauldron. Bromolysergic acid diethylamide was synthesized in the Sandoz laboratories. In a way, this was too bad, for it has provided these doubts. As closely related structurally as it is to lysergic acid diethylamide, it produces little mental disturbance except in very large doses. It has been said that it produces none at all, but two of our staff physicians at the Cleveland Clinic have taken 5 to 7 micrograms per kilogram, per minute and found that it elicits slight mental aberration, though nothing like that produced by lysergic acid diethylamide. Thus, as shown by Cerletti and Rothlin (*27*) in Basel, we have the curious phenomenon that the substitution of one atom of bromine profoundly alters the molecule's effect on the psyche. But even more difficult is the fact that the bromo lysergic acid is an even more potent antagonist of serotonin on the uterus than lysergic acid diethylamide, as my associate from Brazil, L. Sollero, has found (*28*).

Another interesting phenomenon of relevance is that the hypnotic effect of barbiturates is potentiated by serotonin and by reserpine. This phenomenon has been studied especially by Shore, Silver, and Brodie (*29*). These potentiations are blocked by lysergic acid diethylamide. Despite their differing effects, lysergic acid diethylamide and its bromo derivative both block the potentiating effects of serotonin and reserpine (Salmoiraghi, Sollero, and Page, *30*). Introduction of a bromine atom into the molecule of lysergic acid diethylamide thus enhances the serotonin-blocking activity on smooth muscle, but it does not alter its antagonism to serotonin in the central nervous system. Catechol amines have an action similar to that of serotonin in enhancing the action of barbiturate hypnotics.

The problem of the function, if any, of serotonin in brain is far from solved. Its importance currently has been to provide, along with lysergic acid diethylamide, a nidus around which thinking about chemical reactions and the psyche revolve. It is such approaches as these that will, in my view, provide many of the keys to the solution of the problem of mental disease. It has taken phenomena as well as substances of this sort to make neurochemistry real. As I certainly had occasion to know, it was a never-never land until their advent. I personally could not wait, so I took up heart disease as a way to feed my family. In most ways I do not regret it.

I feel impelled at this point both to encourage and to scold the young investigators in this field, especially those coming from the psychiatric disciplines. With the recent acceptance of the principles of neurochemistry has come a wave of uncritical enthusiasm which, if allowed to go unhampered, will almost inevitably lead to grave disillusionment. Without mentioning any names, let me single out one recent episode to illustrate. First comes a highly imaginative and singularly well-written article pointing out, not only the structural similarity between one psychomimetic drug and one not known to have such properties, but also that, on administration of the latter, it was found to be, in fact, psychomimetic. Soon it was heralded as a cause of schizophrenia. Almost inevitably, several serious difficulties have arisen. Others have not been able to repeat the observations, possibly because the substance used originally was not properly defined chemically. Many substances are now being resurrected that are psychomimetic but have no structural similarity. And finally, there is so far no evidence that abnormality in the metabolism of this *x* substance causes schizophrenia.

This is simply to point out that psychiatric research of the chemical sort must, as I have tried to point out before

(*31*), go the long, hard way. No matter how well meaning and how stimulating some of the recent theories may be, we must not get overstimulated in order to forget the hard road under foot. Although, again, I should not single out special cases, I am bound to say that I like the careful approach of the Hoagland group at the Worcester Foundation for Experimental Biology. I do not know whether their view of the great importance of the adrenal glands in the genesis of mental disease is valid, but I do know that their basic research on the problem of adrenal chemistry in relation to neurochemistry will ultimately yield rich dividends. Careful, penetrating investigation, no matter how oriented, has always enriched the value of the world's intellectual stock.

Piperazine Derivatives

I have chosen the piperazine derivatives chiefly because we have recently studied a few piperazine derivatives in both animals and patients, especially 1-(2-methoxyphenyl)-piperazine monohydrochloride. This substance has some antihypertensive properties, but tolerance develops too soon for it to be used as a practical remedy.

It soon became apparent, in the hypertensive patients who received the drug in doses of about 400 milligrams per day, that its effects on the brain were more interesting than its effects on blood pressure. After single intravenous doses, the patients became drowsy or somnolent for about 12 hours. The same result occurred early after oral administration, but in addition, after 2 or 3 weeks of medication, bad dreams occurred regularly in persons who had hitherto been unaware of dreaming at all. In some patients, the dreams were so frightening that the patient became very fearful of going to sleep. While mental confusion and lethargy often occurred, the almost specific nightly experience of dreams was the conspicuous feature of this syndrome.

I have studied the effect of this drug on the arterial pressure responses to a variety of pressor agents in animals. Its most characteristic action is a powerful blocking of phenylalkylamine drugs such as ephedrine, amphetamine, Aramine, Neosynephrine, and Aranthol; it had relatively small effects on adrenaline, noradrenaline, cobefrine, and angiotonin. There is then a mere suggestion that this piperazine derivative might exert its central nervous action by blocking this particular group of phenylalkylamines. I must stress, however, that this type of suggestion may be very misleading without further evidence for such an association.

Other piperazine derivatives have tranquilizing effects and have found important application in medicine, while still others seem to be able to stimulate sympathetic ganglia powerfully. One of the latter is 1,1-dimethyl-4-phenylpiperazinium iodide. Piperazine derivatives, in my opinion, deserve much closer study from the viewpoint of their effects on the chemistry of the nervous system.

The Mind and Neurochemistry

The nature of mind is no clearer today than it was when the problem was propounded by the early philosophers. Much fruitful speculation, and indeed experimentation, has been carried out under the "switchboard" concept of brain function. But the jump from making the switchboard more and more complex until reason appears is one I find difficult to make. Sensation and thought, for example, do not seem to me to be equivalent.

But many must disagree. For example, in a recent article in the *Atlantic Monthly*, G. R. Harrison (*32*) states, "The more flexible electrochemical processes we call thought take place in the new brain, a vast set of switchboards located in the cortex of the cerebrum." Again, ". . . all the glorious welter of color, sound, and emotional involvement of our world results from countless tiny pulses of electricity, and all instinct and awareness appear to be the result of their combinations." And even with assurance he states, "The circuits of the mind improve vastly with use and exercise. Thinking in a given way brings an increased blood supply and more nourishment to the cells and synapses involved." I am not aware of the proof on which these statements are based.

What impresses me more is the confidence many physicists show in their ability to solve the age-old problem of the nature of thought. Feedbacks, cybernetics, molecular memories, and so on are indeed impressive concepts, but so far they carry no conviction to me. The brain is no more than a physical mechanism which, without the mind, is not unlike the so-called "electronic brains" of industry. But without the guiding mind, the brain comes to little. This is not a problem to be approached lightly, for the worlds of belief, of faith, of beauty, and of happiness are at stake.

A materialistic science may not have the methods requisite to the analysis of such a problem. Science has failed before because the problem did not lend itself to analysis by the tools of science, and it can do so again.

Having said this, I now feel free to look more closely at something that is tangible and that is subject to analysis by the usual methods of science. Scientists have been peculiarly reticent about investigating the chemical nature of the brain. It must have occurred to many to do so. What could be more fascinating than to understand something of what goes on in one's own head? Something has held progress back: whether it is the evanescent nature of thought, the Freudian approach, or some vague concept that the brain had no metabolism, I do not know. Certainly, psychiatrists have shown little relish for the mechanistic approach. Curiously, the neurologists have been little better. They have been content to study reflexes and describe syndromes with little concern for the mechanisms of disease which underlie disease. Surely they all knew that adrenaline was a chemical

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which reproduced the results of sympathetic nerve stimulation and that transmission over ganglia is a chemical process. This ought to have been enough to have made them curious about other chemical processes within the nervous system. But not so; until very recently almost nothing has been done in this country at least to further the discovery of such knowledge.

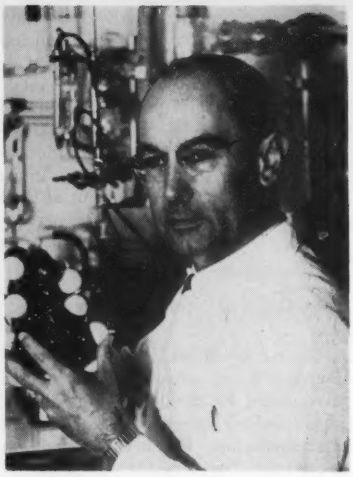
The mind-body dualism has received no solution, but at least it is under investigation. Whether mind is only another property of that remarkable stuff called protoplasm, or whether it is an intangible stuff not lending itself to such material approaches as those of science, will be answered eventually; the point is that the search has started. Whether the brain secretes thought or is only the substrate that provides the means of expressing it is another of the persistent problems. But the least common denominator is that the nervous system requires energy which is chemical, and this is subject to scientific analysis. If we are content to do this competently, a great contribution will have been made.

The recognition of the problem has been a long time in coming from when it was first dimly posed by Thudichum. Thudichum himself was a prophet without honor in the eyes of others. But even in our country there has been little ready acceptance. Biochemists in this country have taken notice of it only in the past ten years at most, and psychiatrists and neurologists in the past three years. The primeval beginnings are still with us.

The close chemical interrelationship between the brain and the body seems to be one that is hard to grasp. Somehow the brain has been dissociated from the body in people's thinking. For this reason, it comes as a surprise that disturbances in brain function can result from diet and that this disturbance may be reflected in chemical disturbances in urine.

For example, Rodnight and McIlwain (*33*) find that the depressive or manic depressive psychosis of pellagra is associated with persistent indicanuria. There seems to be a good basis for associating nicotinamide deficiency and indicanuria because tryptophan can serve as precursor not only of indican but also of nicotinamide. They suggest that indicanuria may represent a diversion of tryptophan from a more essential metabolic route, making the individual more in need of dietary nicotinamide. Another important pathway of tryptophan metabolism is through the formation of serotonin.

Still another interesting example is the metabolic phenomenon of phenylketonuria (phenylpyruvic oligophrenia), in which mental deficiency is associated with an inherited abnormality in the metabolism of phenylalanine. Improvement has been reported in the behavior of patients following use of a diet restricted in phenylalanine. The restriction results in lowering of the high levels of phenylalanine in the blood.



Albert Hofmann, the discoverer of the action of lysergic acid diethylamide [Courtesy of R. Bircher, Sandoz Pharmaceuticals]

It Could Be Philosophy

It has always seemed to me that the chemical approach to the brain is shunned, perhaps among other reasons, from an unconscious fear that is casts doubt on the religious nature of man. My own experience has shown this to be true from the number of unsolicited letters I have received from priests and ministers of all levels of intellectual sophistication, as well as from the public, when my book on *The Chemistry of the Brain* first appeared a good many years ago. Some of these have been inquiring or humble; many have been critical or downright abusive.

The fear must stem from what seems to be a current trend in the direction of dialectical materialism—a trend, I might add, that is at the basis of much anti-intellectualism and animosity toward science. Science has not given man happiness; that is fairly certain. It is a question in a few people's minds just how much it has even improved things. Noble impulses have not followed automatically from the leisure time created by technology.

Science has lost the public mind in a maze of facts and, with them, their inner meaning. Materialistic naturalism is currently prevailing among many of our people as a result of science. This results in a much stronger case for communism than for our free way of life. If man is created entirely materially, then freedom of will has no meaning. If man is wholly a product of natural law, then individual freedom is surely an illusion and the philosophy of communism is a much better solution for his problem than a system that urges a freedom which cannot, and should not, exist.

I wish I knew the solution to this vexing problem of the impact of a materialistic science on the peoples of the world. We can all agree as scientists that it is our prerogative to go as far as is possible with whatever scientific device we know. That prerogative we must never surrender. As scientists, our philosophy of life is no better than that of other thoughtful people, and in some cases it is a good deal worse because of our lack of experience in the much more populous world of intuition and value judgment.

By study of the chemistry of the brain, we seek to define the mechanisms that result in the transmission and integration of nerve impulses and, concurrently, to define their association with thought, no matter what association that may be. The danger quite obviously lies in the nature of the problem of thought itself.

Thought can be influenced by chemical reactions, and it seems to be able to influence them in turn. Thought has been called a property of protoplasm just like any other property, robbing it of its uniqueness. Indeed, as scientists, we go to no little trouble to convince ourselves that thought is just as subject to scientific method as other natural phenomena. It is disturbing to think that it might not be. As a scientist I must confess that, so far, there has appeared not one shred of evidence that it is. I think also that I see more and more circumstances suggesting that it is not subject to methods of analysis as we now know them and to the reproducible experiment.

Might it not be that in this problem we are approaching the ultimate where the same type of problem of causality arises as occurs in the case of the quantum theory and the uncertainty principle? Even measurable data have lost their absolute certainty in this case. But how do we even measure values and emotions that constitute much of the world in which we live?

Is science, as Francis Bacon thought, an image of truth or, better, reality? It is constituted of sense experience, and as neurochemists we should immediately be warned. Sense experience acts as a transport mechanism separating us from reality and possibly correctly informing us of it. Only the images of reality formed and transmitted by the tenuous thread of the nervous system reach consciousness. How close do they mirror

absolute reality? Ask yourself what conception you would have of reality and science if you had been born with a continuous supply of lysergic acid diethylamide.

Scientists are likely to forget that they operate on faith exactly as do religions. Particularly relevant is the fact that the acceptance of any system of logic for thinking about our own sensory experiences is an act of faith. As Vannevar Bush (*34*) puts it, "Our reasoning appears sound to us only because we believe it is and because we have freed it from inconsistencies in its main structure; for it is built on premises which we accept without proof or the possibility of proof."

Pure determinism leaves no place for chance. The configuration of the present moment uniquely and completely determines all the future. My thoughts and actions tomorrow are completely specified by nothing more than the present instant positions and velocities of a myriad of particles of matter and of energy.

I conclude with the hope that, for the small part we play in the shaping of things to come, the neurochemist will pursue his science to its utmost but will never forget that the problem of dualism of body and soul may not be solved in material terms only, and that on its solution hangs the fate of society. The problem must be approached humbly and with care lest ineptitude lead us into the greatest of human tragedies—a philosophy of nothingness; a philosophy without beauty; a philosophy without God. I personally see nothing to persuade me that the functions of the brain are not the functions of protoplasm and that these functions encompass both the material and the transcendant; that there is the necessity to include in the philosophy of biology both those material attributes which are our science and those immaterial attributes which are our values. It is the amalgamation of the two that will close the abyss, which has so destructively separated science from humanity as to make it appear the enemy of man and the enemy of God. In our hearts we know it is neither.

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W. Kaempffert, Science Popularizer

The death of Waldemar Kaempffert, on 27 November 1956, at the age of 79, brought to an end a distinguished career dedicated to the popularization of science. This included 26 years as science editor for the *New York Times,* preceded by a period of equal length as editor and free lance writer of popular science articles. He was one of the first, if not the very first, who made the whole field of science his domain, and one of the very few, and for a considerable time the only one, who could write with authority on developments in all major fields of science, from astronomy to zoology, with clarity and simplicity yet without sensationalism or distortion.

In this respect he set the standards for the modern art of science writing, of which he was for many years the recognized dean. He was the first of the science popularizers who succeeded in making the ever-increasing flow of new-found facts of nature interesting to the lay reader, setting an example on how to steer a clear course between technicality and vulgarization, never bewildering his reader by talking over his head or patronizing him by talking down.

"It is the business of the journalist," he wrote in 1935, "to present the discoveries of the laboratory so that the many will understand. But Heaven forbid that the popularizer should rely too much on emotion. We have passed the stage when gaping wonder can pass for popularization. The facts, simply, humanly and interestingly presented, are what the public wants."

Waldemar Kaempffert was born in New York on 23 September 1877. His parents, Bernhard and Juliette, were of German descent. He graduated at the age of 20 from City College, where he majored in science and was elected to Phi Beta Kappa.

Upon graduation in 1897 he obtained a job as an assistant editor of the *Scientific American,* while at the same time he studied law at New York University. He won his law degree in 1903 and was admitted to the bar, but he never practiced. In 1911 he was named managing editor of the *Scientific American,* and after 4 years at that post he joined the *Popular Science Monthly* as editor, holding that position until 1920.

For some years after 1920 Kaempffert was a free lance writer on popular science. In 1927 he joined the staff of the *New York Times,* for which he wrote a weekly column on current research, occasional editorials on scientific subjects, and sometimes covered scientific conventions and other news events in the field of science.

In 1928 he left New York to become the first director of the new Museum of Science and Industry in Chicago, where he remained until 1931. As director, his ideal was for visitors to leave the museum convinced that scientists did more to "transform the earth and mold institutions than Alexander, Caesar and Napoleon, and that history is made in the laboratory and workshop as well as on the battlefield."

In 1931, Kaempffert rejoined the *New York Times* as science editor, a post he occupied with high distinction until 12 days before his death. His subject matter was properly described to be "as wide as nature itself." It included discussions on the latest concepts of the origin of life, atomic energy, relativity, evolution, nutrition, antibiotics, industrial management, and the effect of dictatorship on scientific progress. He was a strong advocate for the mobilization of scientific research for peacetime, as well as military, goals and was one of the first to champion the organization of cancer research along the same lines as the research laboratories in our great industries.

In 1954, Kaempffert became the first newspaper science writer to receive the Kalinga prize, worth $2800, for which he was nominated by the British Association of Science Writers. A few weeks earlier, he had accepted for the *Times* a special award of the Albert and Mary Lasker Foundation, which credited him with having "shaped profoundly his newspaper's contribution to medical reporting in the public interest." In June 1956, he was named a fellow in the American Society of Mechanical Engineers. Clarkson Polytechnic Institute conferred on him the honorary degree of doctor of science in 1939. He was the author of six books on various aspects of science and served as editor of half a dozen other volumes of popular science, including some for children.

Kaempffert enjoyed telling groups of scientists that the chief function of the science writer was to "make science so clear that the scientists could understand it." He felt that science was "not the property of a learned class but the common possession of mankind." In the words of an editorial in his newspaper, "he had a curiosity that roamed the whole field of human knowledge. A man of strong opinions, he was nevertheless tolerant of all but quackery. His writing, direct and purposeful, was informative and influential. . . . His advice and views were widely sought by educators, by men of the laboratory and of industry."

Those of us who were his colleagues on the *Times* will remember him, as the *Times* editorial states, as a man "who was unpretentious despite his great talents and learning, who could listen well just as he could talk well . . . who worked to the age of seventy-nine with the same zest in search of truth as when he began his career of distinguished specialization more than half a century ago."

WILLIAM L. LAURENCE
New York Times, New York, N.Y.

George Gomori, Leading Histochemist

On 28 February 1957, in Palo Alto, California, George Gomori died suddenly, with symptoms suggestive of coronary thrombosis. Only last October he had moved from the University of Chicago to the Palo Alto Clinic, in order to be nearer to his daughter and grandchildren, and was still in the process of organizing his schedule to resume his investigative work.

Born in 1904 and educated in pathology and surgery at the University of Budapest, Gomori was regarded as being primarily a pathologist, but the bulk of his published works were in histochemistry and histologic staining procedures. His work on the demonstration of the activity of the phosphatases in tissue sections literally initiated a new epoch in morphologic investigation. He and others have extended the basic principles of this work to localize various specific alkaline and acid phosphatases, phosphamidases, lipases, and esterases. He even, on at least one occasion, left the hydrolytic enzymes to extend his investigations to the leucocyte oxidases.

His histochemical work was by no means limited to enzyme localization. His work on enterochromaffin helped to break down the long-held doctrine that this substance was a catechol derivative, and he indicated in his last paper that his own resorcinol hypothesis is perhaps equally tenable with the presently popular serotonin theory, or that perhaps it represents a still unknown substance which differs from both.

Among his more strictly histologic methods, his aldehyde fuchsin procedure has achieved wide usage empirically, and many have attempted to use it as a histochemical procedure. He himself stated that he did not understand its mode of action. This method and his chrome alum hematoxylin method have proved widely useful in identification of pancreatic islet cells in the study of diabetes.

His work on the hydrolytic enzymes has gained world-wide recognition, and he is at this time regarded as having been one of the leading histochemists of the world.

He participated in 1950 in the organization of the Histochemical Society, served on its first council, was its vice president in 1956, and had been elected its president for 1957. He served as associate editor of the *Journal of Histochemistry and Cytochemistry* and of the *American Journal of Clinical Pathology*.

His book, *Microscopic Histochemistry*, though less extensive than its contemporaries, is a model of conciseness and accuracy and has achieved a wide usage.

R. D. LILLIE
National Institutes of Health, Bethesda, Maryland

News of Science

American Science at World's Fair

Howard S. Cullman, U.S. commissioner general to the Brussels World's Fair, which will take place in 1958, has announced plans for the presentation at the fair of a series of notable American scientific achievements. This country's work in four main areas—the cell, the atom, the molecule, and the crystal—will be displayed in the Palace of International Science. A group of American scientists has been appointed to direct and advise on the U.S. scientific contribution to the fair.

The coordinator of scientific exhibits in the Office of the Commissioner General is Alberto F. Thompson, head of the Office of Scientific Information at the National Science Foundation. The foundation will develop and carry out the American science program at the fair.

A Scientific Advisory Committee has been appointed which will function under the general chairmanship of Paul A. Weiss, head of the Laboratory of Developmental Biology at the Rockefeller Institute for Medical Research. Weiss is also chairman of the Sub-Committee on the Living Cell.

Ernest O. Lawrence, Nobel prize winner and director of the Radiation Laboratory at the University of California, will be chairman of the Sub-Committee on the Atom; and Henry Eyring, professor of physical chemistry and dean of the Graduate School, University of Utah, will be chairman of the Sub-Committee on the Molecule.

The chairman for the Sub-Committee on the Crystal will be Cyril S. Smith, professor of metallurgy and director of the Institute for the Study of Metals at the University of Chicago, and Frederick Seitz, professor of physics at the University of Illinois, will serve as cochairman. An additional group of American scientists has been named to the four subcommittees, and other scientists will be working on the fair project both at the National Science Foundation and elsewhere.

No final decisions have yet been made about the exhibits. However, for the atom, there is a plan to show the bombardment of the earth by cosmic rays in a large cloud chamber in which the radiation particles appear as streaks of rain. Also in the atom section will be a demonstration of Willard F. Libby's carbon-dating method.

In the crystal section there will be a transistor display. The development of single-crystal "whiskers," which are even smaller than transistors but serve many of the same purposes, will also be shown.

In the molecule section the rapidly growing knowledge of the structure of these submicroscopic bodies will be exhibited. In the living cell section, a display that will utilize atomic tracer elements will demonstrate how a single green leaf produces all the necessary components of plant life through the photosynthesis of the minerals from the earth, the gases from the atmosphere, and the energy from the sun.

Smithsonian Ecuadorian Expedition

Recently discovered archeological sites in Ecuador show that the prehistoric cultures of Ecuador had important influences on cultural development in Peru and the Amazon Valley before the arrival of the Spanish in the 16th century. These findings are the result of 4 months of field work on the Río Napo in the eastern lowlands and in the Guayas Province on the coast of Ecuador by Clifford Evans, associate curator, Division of Archeology, U.S. National Museum; Betty J. Meggers, research associate, Smithsonian Institution; and Emilio Estrada, director of Museo Arqueologico "Victor Emilio Estrada," Guayaquil, Ecuador. The work was conducted under the auspices of the Smithsonian Institution and the Casa de la Cultura Ecuatoriana, Nucleo del Guayas, with the aid of a research grant from the American Philosophical Society.

Excavations undertaken on the Río Napo revealed large villages and a well-developed ceramic art, which included elaborate vessel forms and complex decoration by incising, painting, and champleve (that is, with the design background cut back from the original surface). This pottery has close resemblances to the pottery from the island of Marajó at the mouth of the Amazon. The Marajó culture is alien and seems out of place at the mouth of the Amazon, and its origin has until now been unknown. The work of Evans and Meggers indicates that this culture originally came from the headwaters of the Amazonian tributaries in Ecuador and Colombia. This is the first time that such an extensive downriver migration in prehistoric times has been proved by archeological evidence in South America. The movement probably took place a few hundred years before the arrival of the Spanish. When Orellana made his voyage down the Napo and the Amazon in the mid-16th century, the sites along the Río Napo had already been abandoned, and he found no Indians living on that river within the area embraced by the present boundaries of Ecuador.

Archeological investigations by Evans, Meggers, and Estrada in the Guayas Province of coastal Ecuador have revealed the presence of two early cultures whose characteristics show many close similarities with the early cultures of Mexico and Peru. The oldest of these has been named the Valdivia culture. The pottery of the Valdivia culture shares with the earliest pottery-making cultures of Meso-America (Mexico and Central America) distinctive traits like broad-line and fine-line incision, excision, rocker stamping, and highly polished vessel surfaces.

A large number of female figurines made of pottery indicate the existence of a religious complex. These figurines have elaborate hairdresses, suggesting that women even at this ancient time paid a great deal of attention to their coiffures, even though they were nude. Sometimes the body was painted red in various designs. Pottery of a similar style has been found in Peru, but it does not resemble that of the early cultures of Meso-America as closely as does the Valdivia culture from coastal Ecuador. This suggests that the movement that distributed this early Formative Period culture so widely from Mexico to South America traveled from north to south. The Valdivia culture must therefore be at least as old as the similar culture in Peru, which has been dated by carbon-14 as between 1500 and 1000 B.C.

Following the Valdivia culture, Evans, Meggers, and Estrada have discovered another early culture with different features, but which also resembles closely cultures in Meso-America and Peru. This has been called the Chorrera culture and has as characteristic features thin, highly polished red and black pottery, very fine incised lines, rocker stamping, and bottles with tapered spouts and handles decorated with whistle. These traits are shared with the Formative Period cultures of Tlatilco in Mexico and Chavin and Cupisnique in Peru. As in the Valdivia culture, the Ecuadorian pottery more closely resembles the Mexican than the Peruvian expression of this wide-

spread horizon, indicating in this case also that the movement was from north to south. This culture is dated from 1000 to 500 B.C.

The discovery of these two early Ecuadorian cultures is significant because it provides definite evidence of the north-south direction of movement in this early prehistoric period. Prior to the work of Evans, Meggers, and Estrada, the origin of many traits in Peru could not be adequately explained, and the relationship between the early cultures with similar characteristics in Mexico and Peru could not be determined. The archeological investigations in Ecuador thus represent an important contribution to the solution of major problems in New World prehistory.

Baghdad Nuclear Center

King Faisal of Iraq recently opened the Baghdad Pact Nuclear Center at Shalichiyah, near Baghdad. The center includes a teaching laboratory for post-graduate courses of the same standard as the isotope school at Harwell, England, and has enough electronic and radiochemical equipment for the training of 20 students in peaceful uses of the atom. Britain furnished most of the necessary technical equipment, with Iraq supplying buildings. Instruction began this month.

Sir John Cockroft, Britain's atomic energy chief, has been elected chairman of the Baghdad Pact's scientific council. The first director of the center and four of the scientific staff are from Harwell.

MIT Earth Sciences Lab

Massachusetts Institute of Technology has set up a laboratory of earth sciences to study this planet's solid interior, the atmosphere, the oceans, and the land masses between. The laboratory will be operated jointly by the departments of meteorology, geology, and geophysics and is expected to become a research center for geologists, geochemists, geophysicists, meteorologists, and oceanographers.

Handbook of Mathematical Tables

The National Bureau of Standards has begun preparation of a *Handbook of Mathematical Tables*. In addition to the elementary functions, the *Handbook* will cover almost the entire field of transcendental functions. Expected to be ready before the end of 1958, it will appear as a volume of about 1000 pages—750 pages of tables, 50 pages of graphs, and 200 pages of text.

The project is supported by the National Science Foundation, and is being carried out by the bureau's computation laboratory and numerical analysis group. Correspondence regarding the *Handbook* should be addressed to Dr. M. Abramowitz, National Bureau of Standards, Washington 25, D.C.

Ford Aids Woodrow Wilson Fellowship Program

In an effort to combat the shortage of college teachers, the Ford Foundation has announced a $25-million appropriation for a large-scale extension and development of the National Woodrow Wilson Fellowship Program. This action will support a broad program to attract able college students into the academic profession and will provide graduate fellowships to potential college teachers at the rate of 1000 a year for the next 5 years.

Individual awards, which will be applied to tuition and living expenses for the first year of graduate study, are expected to average $2200 and will require approximately $11 million of the total appropriation. Another $10 million will go to universities for aid to graduate students beyond the first year. A nationwide recruiting program will absorb about $2.8 million, and administrative expenses over the 5-year period are expected to be $1 million.

Out of the total funds appropriated, $200,000 will be made available to the Association of American Universities and its affiliate, the Association of Graduate Schools, to provide for an immediate increase of 100 Wilson fellowships for the fall of 1957—a 50-percent rise over the 200 awarded this spring. The $200,000 will be paid to the University of Michigan as fiscal agent. The present national headquarters of the Woodrow Wilson organization is in Ann Arbor, Mich.

To conduct the expanded recruitment and fellowship program planned for the next 5 years, the organization is being reconstituted as a nonprofit corporation, the National Woodrow Wilson Fellowship Corporation. The independent governing board is to be made up of a combination of laymen and educators. Board members and executive officers will be announced later.

The recruitment program will be conducted largely through a corps of 100 or more faculty members, who will give approximately one-third of their time to stimulating faculty cooperation on approximately 1000 college campuses. Four or five full-time regional field directors will assist in developing and coordinating the program.

Nominations for Woodrow Wilson fellowships will be made by local faculty members, and selection will be made by regional committees and a national committee made up of active university and college faculty members. Fellowship recipients may, in general, attend the institutions of their choice and will be free to select their own fields of study. Awards formerly were made only in the humanities and social sciences. The new program includes the natural sciences and mathematics as well.

The $10 million allocated for assistance beyond the first year will be used for grants of $2000 each to the university at which each fellow enrolls. Three-fourths of this amount must be used for financial aid to graduate students, particularly in their final year. The aid provided by this stipend is at the discretion of the university, and it is not limited to Wilson fellows. The remaining one-fourth may be used by the university for additional fellowships or for strengthening its graduate program generally.

The Woodrow Wilson fellowships were initiated in 1945 by Princeton University. In 1952 a national organization was formed under the sponsorship of the Association of American Universities to conduct an expanded program. Prior to the Ford Foundation action, the Carnegie Corporation and the General Education Board of the Rockefeller Foundation supported it with grants of funds totaling $1,150,000.

Rand on Fallout

A detailed description of how radioactive products of nuclear explosions are borne aloft and fall to earth in the vicinity of the explosion and for several hundred miles downwind appears in a paper published by three scientists of the Rand Corporation of Santa Monica, Calif., in a recent issue of the *Journal of Meteorology*, official publication of the American Meteorological Society. The findings, recently declassified, were reported by William W. Kellogg, Stanley M. Greenfield, and R. Robert Rapp. Their paper, "Close-in fallout," is the result of research by Rand for the Atomic Energy Commission.

Rand has programmed the problem of computing the fallout from an atomic cloud for solution on a high-speed electronic digital computer (IBM-701). The computer is given the appropriate wind structure and atomic-cloud dimensions, and proceeds to calculate the location on the ground of 10,000 radioactive particles which are judged to be representative of the atomic debris. The machine takes approximately 1 hour to make this calculation.

In an effort to equip the civil defense planner with a ready means for estimating the probable distribution of fallout

and the dose rates (measured in roentgens per hour) that can be expected on the surface at various distances from ground zero, Rand has published a *Catalog of Fallout Patterns* (RM-1676-AEC) by Greenfield, Rapp, and Patricia A. Walters. This catalog portrays fallout patterns covering four levels of bomb yield and some 20-odd typical wind situations.

The civil defense expert may construct, on coordinate paper, a wind "structure" indicating wind direction and force at various altitudes, from conventional and readily available observations of radiosonde balloons. Matching this structure by eye against an index of wind structures in the catalog, he selects the one that fits and is able to depict the fallout patterns associated with that wind situation. These patterns —most of them cigar-shaped, stretching downwind from ground zero—provide him with estimates of the dose-rates to be expected from an atomic explosion. For example, it would show that a 1 megaton bomb falling on a U.S. city under typical June winds condition would deposit a lethal doze of radioactive debris 20 miles downwind; people would be made ill as far as 100 miles downwind.

Marlborough Man

Reconstruction of the skull of the "Marlborough man," whose fossilized skeleton was discovered at Salisbury, Rhodesia, in 1956, has been completed by E. Trevor Jones. In an article in the *Central African Journal of Medicine,* he comments that the skull is that of a man "not resembling any existing race living in Africa today." Some features of the bone structure, he points out, differ from those of both the European and the Bantu. The Marlborough man had a large head and heavy jaw similar to that of the Boscop man discovered in South Africa.

Oldest Hospital and Medical School Unite

An agreement of affiliation between the Pennsylvania Hospital's Department for Sick and Injured, Philadelphia, and the University of Pennsylvania School of Medicine has been announced. It will be effective in September. This joint action is an agreement of professional affiliation between the staffs of the two institutions. The affiliation unites in a close working relationship Pennsylvania Hospital, the nation's first hospital, founded in 1751 by Benjamin Franklin, and the nation's first school of medicine, established in 1765 at the University of Pennsylvania, which also had been founded by Franklin.

The first teaching of medicine in the United States was done on the wards of the Pennsylvania Hospital, and the students from the University of Pennsylvania School of Medicine have been taught there ever since the school was founded. The new agreement, discussions of which were first held about 1800, now places official seal upon a mutually cooperative educational effort that has been in effect for almost two centuries.

Dentistry Survey

A 2-year survey of dentistry in the United States will begin this year under the direction of a commission headed by Arthur S. Flemming, president of Ohio Wesleyan University and until recently director of the Office of Defense Mobilization in Washington. The announcement of Flemming's appointment was made by the American Council on Education, which is conducting the $400,000 survey at the request of the American Dental Association. The first four members of the commission that will serve with Flemming are as follows: Lawrence A. Kimpton, chancellor, University of Chicago; W. Howard Chase, president, Communications Counselors, Inc., New York; Willard C. Fleming, dean, School of Dentistry, University of Pennsylvania; and Charles P. McCormick, chairman, McCormick and Company, Baltimore.

The commission membership will reflect not only the broad interests of the dental profession but also the interests of those whom the profession serves. The commission will select a director of the survey. His staff, at headquarters in Chicago, will include an assistant director, five or six technical and editorial staff associates, and a secretarial and clerical staff of six to eight persons.

The commission will be assisted in specific areas of the work by four committees: dental education, dental research, dental health, and dental practice. The survey is financed by grants as follows: the Kellogg Foundation, $250,000; Americal Dental Association, $120,000; Rockefeller Brothers Fund, $25,000; and the Louis W. and Maud Hill Family Foundation, $5000.

Radioactive Minerals in India

The Atomic Energy Department, Bombay, India, has announced discovery of large radioactive mineral deposits "somewhere in northern India." The announcement said that the deposits are even richer than those of the Travancore sands in southern India, and that investigations so far show that 3.3 million tons of ore contain 300,000 tons of thorium and 10,000 tons of uranium of 10 percent and 0.4 percent concentration, respectively.

Mathematics Camp

The University of Kansas will hold its second annual Science and Mathematics Camp on the campus, 16–28 June. This is one of a very few such camps. At Kansas attendance is limited to 80 high-school sophomores, juniors, and seniors.

The purpose of the camp is to acquaint the participants with the various scientific areas, with the aim of interesting able high-school students in a career in science. Fifteen different sciences are represented on the program.

Some scholarship aid is available. The camp staff is derived from the university's faculty. For 1957, the camp director is D. Paretsky of the department of bacteriology, and the associate director is C. H. Phoenix of the psychology department.

U.S. Invitation to U.N. Nuclear Conference

The United States has invited the United Nations to hold its second atoms for peace conference, scheduled for 1958, in Chicago. The tentative plan has been to meet again in Geneva, as in 1955. However, in a letter to U.N. Secretary General Dag Hammarskjold, United States Ambassador James J. Wadsworth, who has been in charge of American policy at the U.N. on peaceful uses of the atom, said that Chicago "would consider it a great honor to be permitted to play host to this great international event."

International Zoonoses Center

The first international center for studying animal-borne diseases affecting man was recently dedicated in Azul, Argentina. The Pan American Zoonoses Center, which is planned as a clearinghouse for scientific knowledge from many lands, will be concerned with testing vaccines and other biologicals, training personnel, and furnishing consultation services by pooling the talents of physicians, veterinarians, and public health officials.

There are approximately 100 zoonoses, and in this country some of them present a problem that is coming to the forefront as a public health hazard. In recent years, more than 80 zoonotic diseases, including brucellosis and toxoplasmosis, have been detected in the

United States. In Texas, for example, not long ago 143 cases of psittacosis were reported in a single week. At the same time, a serologic survey in Colorado disclosed that nearly one-fifth of all persons under 30 were likely to have a positive reaction for Western equine encephalitis.

Nuclear Tests to Start

The Atomic Energy Commission has announced that the 1957 series of low-yield nuclear detonations at the Nevada Test Site is scheduled to begin on about 15 May. No termination date can be established at present, but it is expected the test site will be used intermittently throughout the summer.

The site will also be used for experiments related to the safety of nuclear weapons during handling and storage. Since there will be no nuclear detonation for these tests, there are not expected to be any effects outside the immediate area.

The operations at the test site will be conducted by the Nevada Test Organization, of which James E. Reeves of the commission's Albuquerque Operations Office is test manager. Most of the staff of the Las Vegas Branch Office has moved to the site, and a majority of the test organization personnel from other offices and units are scheduled to be at the site by about 1 May. Tests during the 1957 series, known as Operation Plumbbob, will be scheduled at greater intervals than during the 1955 series to make allowance for delays that may result from weather conditions, to avoid overcrowding in housing available at Camp Mercury, and to permit a greater length of time for completing construction work.

Research Facilities Grants

The U.S. Public Health Service has announced approval of 35 grants totaling $3,974,943 to help 27 research institutions in 18 states build additional facilities for research in cancer, heart disease, mental illness, and other major illnesses. The grants were recommended by the National Advisory Council on Health Research Facilities, which reviewed 165 applications amounting to about $66,384,500. Applications for grants will again be considered by the council 27–29 May.

Congress last year authorized $30 million a year for 3 years in grants to research institutions on an equal matching basis for the construction and extension of research facilities. The law also established the advisory council, which now has approved 109 grants totaling approximately $30 million.

Atomic Power in Northern Ireland

An announcement has been made that an atomic power station of 150 megawatts will be established in Northern Ireland, a country with a population of only about 1,400,000. The station should be in operation by 1963 or 1964. It will cost about £25 million ($70 million). Relating cost to resources—the revenues of the government in the current financial year total £93 million ($260.4 million)—it is easy to see that this investment by Northern Ireland is on a scale that is probably unparalleled by any other country.

Augmentation of electricity services has been made necessary by the tremendous increase in demand that has resulted from Northern Ireland's industrial development program. This program includes the establishment of factories by such firms as Du Pont and Chemstrand.

Wayne Offers Master's Data Processing

Wayne State University will be the second school in this country to offer a master's degree in automatic data processing. Harvard University is the other school. The new program, which begins in September 1957, will incorporate the management sciences—economics, mathematics, accounting, and computing.

Registry of Pediatric Pathology

Under the auspices of the American Academy of Pediatrics, a special registry devoted to pediatric pathology is to be established as one of the components of the American Registry of Pathology of the Armed Forces Institute of Pathology. The success of other component registries in collecting source material for the study of rare and unusual diseases in several branches of medicine has prompted the Armed Forces Institute to devote a special section to the pathology of diseases of children.

The Registry of Pediatric Pathology will limit its material only with respect to the age group involved. Adequate cataloging, maintenance of records, and availability of material are primary objectives. In addition, a consultation service will be provided for all pathologists similar to that offered by the other component registries. Specialists in pediatric pathology in this country and abroad will thus be on call for questions in their particular fields of interest. The material will also be made available for teaching purposes, and it is hoped that in the future the registry may provide a position for training in pediatric pathology.

The support of all pathologists and pediatricians is needed to insure the success of this new division. All inquiries should be addressed to the Registry of Pathology, Armed Forces Institute of Pathology, Walter Reed Medical Center, Washington 25, D.C.

Louisiana Veterinary Center

The $600,000 Veterinary Medical Research Center at Louisiana State University was dedicated recently. It consists of six animal laboratory buildings and a large two-story addition to the Dalrymple Memorial Laboratory. Research has already begun on anaplasmosis, leptospirosis in cattle and swine, gastrointestinal parasites of cattle, and bibriosis, a disease of the reproductive system. Anaplasmosis, which results in death for 40 percent of the infected animals and causes an estimated $10 million annual loss in southern states, will be one of the major research projects. The disease is characterized by a rapid reduction of red blood cells.

In addition, respiratory diseases of poultry as they affect the blood-cell system will be studied from the standpoint of developing a diagnostic test. The research will be conducted in a separate building which contains four isolation units. One of the other buildings will be used for the study of animal diseases that are highly contagious. Its construction will permit 11 separate studies to be conducted simultaneously in individual isolation units. Nine investigators are now working at the laboratory and several more are to be added to the staff in the near future.

New Westinghouse Unit

The Westinghouse Research Laboratories has announced formation of a new scientific group to expedite the development of electronic and related devices. The group is already operating in what is to be known as the physics project laboratory. The function of the new unit is to bring into final practical form at an accelerated rate the variety of devices that are being conceived as a result of the company's regular program of research.

Among the projects assigned to the group is the continued development of the image multiplier tube, a new type of electronic tube recently announced by the laboratories. The laboratory will also be concerned with the immediate development of certain classified electronic projects for the Government.

The head of the new laboratory is A. E. Anderson, formerly executive staff assistant to J. A. Hutcheson, Westing-

house vice president in charge of research and engineering. R. O. McIntosh has been appointed section manager in charge of tube laboratory operations. R. W. Decker and M. M. Wachtel are project supervisors. The Westinghouse Research Laboratories' present electron tube laboratory will be incorporated into the new organization.

Rehabilitation Institute

Washington University is planning to build a $675,000 rehabilitation institute to serve disabled persons in the St. Louis metropolitan area. The new facility will be named for the late Mrs. Irene Johnson, one of the principal donors of funds. In addition to work with patients, the institute will train personnel in rehabilitation procedures and develop new methods of treatment. An active research program relating to chronic disabilities will also be carried on.

The new building will house the departments of physical and occupational therapy now located in other buildings in the Washington University Medical Center. Robert E. Shank, professor of preventive medicine in the School of Medicine since 1948, will be director of the institute.

U.S. Population

A United States population of 178½ million by the time of the 1960 census is predicted by the statisticians of the Metropolitan Life Insurance Company. In that event, the 1950's will show a population increase of about 27⅓ million, or two-fifths more than the 1940's, which up to that time had the greatest gain for any 10-year period.

In the 11⅓ years since World War II, almost 29½ million people have been added to our population, which is more than the gain during the 23 years between World War I and World War II.

During the year just ended, the population, excluding the Armed Forces overseas, increased by 1.8 percent. Every geographic area shared in this growth, but the Far West showed the highest rate of increase—almost double the national rate.

Since the 1950 census, California has gained more than any other state—about 3.1 million inhabitants. California's population has now reached approximately 13.7 million, which is exceeded only by New York State. Nevada, Arizona, and Florida have experienced rapid population growth, and increases well above the average rate for the country have occurred in Delaware, Maryland, and Michigan. Losses in population have been sustained since the 1950 census in five states: Arkansas, Mississippi, West Virginia, Vermont, and Maine.

Metropolitan Life also reports that the average length of life among its industrial policyholders rose to a new high of 70.2 years in 1956. This is slightly above the figure for 1955 and represents an increase of 24 years since 1909.

For nearly two generations, the average length of life has been increasing more rapidly among American wage earners and their families than for the general population of the United States. In 1909, the average lifetime of Metropolitan's industrial policyholders was about 6 years less than that for the population as a whole. Since then, the disparity has been narrowing; at present the two groups are on a par.

Scientists in the News

ROBERT B. WOODWARD of Harvard University, who has been a leader in the synthesis of quinine, cortisone, lysergic acid, strychnine, and reserpine, and C. GARDNER SWAIN of the Massachusetts Institute of Technology, well-known investigator in theoretical organic chemistry, were given $1000 prizes in chemistry during the recent national meeting of the American Chemical Society in Miami, Fla. Woodward was the first recipient of a new honor, the ACS award for creative work in synthetic organic chemistry, sponsored by the Synthetic Organic Chemical Manufacturers Association. Swain, who has carried out original laboratory research and mathematical correlations that make it possible to predict the speed of many chemical processes, received the Precision Scientific Company award in petroleum chemistry. Among other awards presented during the ACS meeting are the following:

The first James T. Grady medal, given by the society for distinguished reporting of chemical progress, was presented to D. H. KILLEFFER of Crestwood, N.Y. A chemical engineer and writer, Killeffer has been, for more than 30 years, a leader in the interpretation of chemical advances to the layman. He has written many magazine articles on chemical subjects and also several books.

HAROLD A. SCHERAGO, associate professor of chemistry at Cornell University and specialist in blood clotting, received the $1000 Eli Lilly and Company award in biological chemistry. Scherago, whose work on protein chemistry is gaining wide recognition, was awarded a Fulbright grant and a Guggenheim fellowship last year to permit him to do advanced research in Copenhagen, Denmark. He is spending the current academic year there.

GILBERT J. STORK, professor of chemistry at Columbia University, received the $1000 ACS award in pure chemistry for his extensive research on the synthesis of such natural products as compounds of the morphine family and the steroids, a group of substances that includes cortisone and the sex hormones.

D. H. R. BARTON of the University of Glasgow (Scotland), specialist in the structure of natural products, received the $1000 Fritzsche award for his investigations of complex terpenes, chemical substances derived from trees and plants and used in the manufacture of camphor, perfumes, and medicines. His work in this field has elucidated many problems in the chemistry of essential oils.

LUCY W. PICKETT, head of the chemistry department of Mount Holyoke College, received the $1000 Garvan medal, presented each year to an outstanding woman chemist.

CHARLES R. HAUSER, professor of chemistry at Duke University, won the 1957 ACS Florida Section award for his contributions to modern theories of organic chemistry and for his demonstrated ability as an educator during a 29-year teaching career at Lehigh University and Duke.

CARL O. SAUER, professor of geography on the Berkeley campus of the University of California, has recently been selected to receive the Vega medal in gold, the most highly regarded honor in the sciences of the earth and sea. The medal is an award of the Swedish Society for Anthropology and Geography and is traditionally presented by the King of Sweden on Vega Day, 24 Apr., in Stockholm. Sauer is being honored for his "investigations into man's utilization of the surrounding geographical milieu during various cultural epochs." He is the fourth American who has received this medal since its inception in 1880.

GEORGE R. COWGILL, professor of nutrition at Yale University, has received the $1000 Osborne and Mendel award for 1957, which is administered by the American Institute of Nutrition. He was honored for "his many pioneer and subsequent fundamental research contributions to our knowledge of the B-vitamins and of protein nutrition; and for his numerous other broad contributions to the science of nutrition as a teacher, as editor of *The Journal of Nutrition*, and as an expert advisor in this field."

JOHN C. CLARK, who has helped direct most of the nation's atomic weapons tests since 1946, has been appointed staff assistant to J. R. Dempsey, manager of Convair-Astronautics. Clark has resigned as associate leader of the Test Di-

vision at Los Alamos Scientific Laboratory to accept the Convair post. He will be concerned with research and development testing of the Atlas intercontinental ballistic missile. The Atlas ICBM is under development at San Diego, Calif., by the Convair Division of the General Dynamics Corporation.

Clark played a major role in establishing the Pacific Proving Ground at Eniwetok and the atomic proving ground at Frenchman's Flat, Nev. He was in direct charge of many of the weapons tests conducted at both sites. The task of disarming a nuclear device that failed to explode fell to him during one of the Nevada tests, an event that was widely publicized.

RAYMOND EWELL, former assistant director of the National Science Foundation, has been named vice chancellor for research and professor of chemistry at the University of Buffalo, effective next September. Last July the Ford Foundation made Ewell's services available as a consultant to the Indian Ministry of Commerce and Industry in New Delhi. In this capacity he holds a post as development officer of economic surveys. He served in a similar capacity in the Philippines during 1955.

E. E. SNELL, professor of chemistry and associate director of the Biochemical Institute of the University of Texas, has been named professor and head of the biochemistry department at the University of California, Berkeley.

REBECCA H. SPARLING, who is in the engineering department of Convair, a division of General Dynamics, at Pomona, Calif., has received the annual award of the Society of Women Engineers. At Convair she is concerned with new developments in materials and processes for the design and manufacture of guided missiles and other special ordnance weapons for the Navy.

HILARY KOPROWSKI, since 1946 assistant director of viral and rickettsial research for the Research Division of the American Cyanamid Company, Lederle Laboratories, Pearl River, N.Y., has been appointed director of the Wistar Institute of Anatomy and Biology, Philadelphia, Pa. He will take up his new duties on 1 May, when he will head an accelerated program of research devoted to study of the single cell.

Koprowski, whose appointment fills a post that has been vacant since the retirement of MILTON J. GREENMAN, has made noteworthy contributions to research on rabies and poliomyelitis. He has developed a living virus chick-embryo vaccine for preventing rabies, and his polio studies stimulated research in the use of the living virus as an immunizing agent. Koprowski is expected to expand the institute's studies in the fields of geriatrics and cancer.

CHARLES SHEARD of the Mayo Clinic in Rochester, Minn., will receive the Edgar D. Tillyer medal of the Optical Society of America during its meeting in Columbus, Ohio, next October. The medal, which is granted every 2 years, is being given to Sheard for his research in physiological optics.

W. M. BEVER has been named head of the department of plant pathology at the University of Illinois, effective 1 Sept. Bever has been at Urbana since 1940 working for the U.S. Department of Agriculture on cereal diseases. He was appointed to the university faculty in 1949.

WILLIAM M. GROSVENOR, JR., chemical engineering consultant, has been appointed director of research and development for the American Sugar Refining Company, 120 Wall St., New York.

CHARLES J. STRICKLER has been appointed section head of organic chemistry in the chemistry department of Horizons Incorporated, Cleveland, Ohio. Strickler obtained his industrial experience at the Abbott Laboratories of Chicago, Ill., the Michigan Chemical Corporation of St. Louis, Mo., and the Diamond Alkali Corporation of Cleveland, where he gained broad experience in the field of pharmaceuticals, barbiturates, anesthetics, and fine and heavy organic chemicals.

H. RUSH SPEDDEN has been appointed director of research for the Union Carbide Ore Company, a division of the Union Carbide and Carbon Corporation. He will be responsible for the company's operations in the corporation's Nuclear Research Center in Sterling Forest, N.Y. There he will direct investigations that will cover the entire range of activities from mineralogy and geology to new mineral prospecting methods, including work in geophysics and geochemistry. Other work will be concerned with research on extracting metals from ore bodies. Since 1952, Spedden has been in charge of the minerals research department of the corporation's Research Laboratories at Niagara Falls, N.Y.

EARL D. BOND of Philadelphia has been appointed by the Menninger Foundation, Topeka, Kan., as its first Alfred P. Sloan visiting professor in psychiatry. Bond is a former president of the American Psychiatric Association.

Col. FRANCIS E. COUNCIL, Medical Corps, U.S. Army, retired on 1 Apr. after having completed more than 30 years on active duty. He served as deputy director (Army) of the Armed Forces Institute of Pathology and as chief pathology and allied sciences consultant to the Surgeon General of the Army from December 1955 until his retirement. Council has gone to Fort Worth, Tex., where, as a pathologist, he will be associated with John J. Andujar of the Fort Worth Medical Laboratories. Col. JOE M. BLUMBERG, MC, USA, has succeeded Council as deputy director of the AFIP.

Council received his B.S. degree in 1921 from Texas Christian University and instructed in biology at that institution from 1921 to 1922. After receiving his M.D. degree in 1926 from Vanderbilt University, he began his long career in the Army Medical Service. Following graduation from the Army Medical School and the Medical Field Service School in 1929, he was chief of the Division of Biological Products and instructor in immunology at the Army Medical School from 1933 to 1937. He graduated from the advanced graduate course of the Army Medical School in 1937, and was awarded a doctorate in public health by the Johns Hopkins University in 1938.

His duties as a medical officer in the Army Medical Corps prepared him for a series of assignments as commanding officer of various Army laboratories.

ALBERT R. MEAD, professor of zoology at the University of Arizona, has been appointed acting head of the department of zoology. He succeeds the late GEORGE T. CALDWELL, department head since 1936, who retired on 1 July 1956.

ALAN BELCHER, former deputy commissioner of the Royal Canadian Mounted Police, has accepted the post of executive director of the Arctic Institute of North America. He assumed his new duties on 1 Apr. at the headquarters of the institute in Montreal.

ROBERT R. SEHNERT, a physicist, has been appointed eastern representative for Atomics International, a division of North American Aviation, Inc. His office will be in Washington, D.C. Formerly applications engineer at Atomics International's headquarters in Canoga Park, Calif., Sehnert was primarily engaged in programs related to the sodium reactor experiment, sodium graphite atomic power plants, and research reactors being built by the company for the Danish Atomic Energy Commission and the Japan Atomic Energy Research Institute.

Reports

Carbutamide and Plasma Insulin Activity

For about two years, arylsulfonylurea derivatives—for example N-*p*-aminobenzene-sulfonyl-N′-*n*-butyl-urea (Carbutamide, *1*), have been used in the therapy of human diabetics. It is supposed by different authors that an inhibition of glucagon production represents the mode of action of Carbutamide (*2*). However, the morphologic appearance of the islets of Langerhans, as well as the known metabolic effects produced by Carbutamide drug, is not in agreement with such a mechanism of action (*3–5*). Whereas α-cell destruction by Synthalin or *p*-aminobenzene-sulfonamide-5-isopropyl-1,3,4-thiodiazole (IPTD) in alloxan-diabetic animals causes a normalization of the metabolic disturbance (*6*), Carbutamide does not influence the hyperglycemia and glycosuria of alloxan-diabetic rats. The absence of a curative effect of Carbutamide in alloxanized (*3, 5, 7*), pancreatectomized (*8*), metasteroidal (*4*), or metahypophyseal (*8*) animals and the effectiveness of Carbutamide in normal or idiosteroidal rats (*3, 5*) point to the probability that the endogenous production of insulin may be indispensable for the blood sugar-lowering effect of the substance.

Previous experiments have shown that, under the influence of Carbutamide, the β-cells of the islets of Langerhans exhibit morphological changes indicating an increased activity of this system (*3–5, 9*). In long-term experiments, this stimulation results in a relative β-cell insufficiency as manifested by an impaired sugar tolerance in rats and dogs. In these animals, an increased diameter of β-cell nuclei and an enlargement of the islets with degranulation and occasional hydropic degeneration of the cells may be observed (*5*). In addition, Carbutamide causes a stimulation of the adrenal cortical activity which is indicated by a moderate "progressive transformation" (Tonutti, *10*) of the cortical zones, as well as by depletion of ascorbic acid (*3, 5*).

A stimulation of the insulin production is supposed to be followed by an increased level of blood insulin. Therefore, insulin activity of plasma in animals that had been treated with Carbutamide was investigated. Insulin assays were performed by the method of Randle (*11*). Instead of determining the glucose uptake of the isolated diaphragms, we measured the increase of glycogen synthesis, using the anthrone method of Seifter *et al.* (*12*).

The results (Table 1) show that Carbutamide produces a highly significant increase of insulin activity in normal animals, corresponding to the decrease in blood sugar level after a single dose of Carbutamide. In rats treated daily with the drug over a period of several months, no increase in plasma insulin activity was observed, according to the lack of blood sugar-lowering effect of the substance after continuous administration. The increase in muscle glycogen synthesis produced by insulin is not seen when Carbutamide is added to diaphragm *in vitro* (*13*). Therefore, the insulinlike effect of plasma of Carbutamide-treated rats on diaphragm glycogen cannot be attributed to a direct action of Carbutamide on diaphragm.

Our results indicate a stimulating effect of Carbutamide on insulin activity in short-term experiments. In addition, it was observed that continued stimulation of the β-cell system by Carbutamide is followed by a relative insufficiency of these cells, expressed by a lack of additional insulin output and the previously described decrease in sugar tolerance (*5*).

Besides certain morphological signs of enhanced β-cell activity (*3–5, 9*) the islets of rats that are repeatedly treated with Carbutamide or Tolbutamide (N-toluene-sulfonyl-N′-*n*-butyl-urea, *14*) (500 mg/kg daily for 3 weeks orally) exhibit an increased mitotic rate of β-cells.

The increase of insulin secretion described in a previous paragraph cannot fully account for the metabolic effects produced by Carbutamide and Tolbutamide. The lack of difference in the response of normal and hypophysectomized rats to the blood sugar-lowering activity of sulfonylurea derivatives (*15, 16*), as well as their insulin-sparing effect in pancreatectomized dogs (*8*) or alloxanized rats (*5*), and the increase of

Table 1. Plasma insulin activity (milliunits in 0.5 ml) and blood-sugar decrease (milligram percent) in Carbutamide-treated rats. In every group, 2-ml portions of plasma of two rats (male albino Sprague-Dawley rats of weight 280 to 330 g) were pooled, and the insulin activity was tested with four or five hemidiaphragms. Blood sugar estimations in plasma donors were performed before the ingestion of the drug and at the time of insulin determination. The significance of differences in insulin content was as follows: groups I and II, $P = 0.001$; groups I and III, no difference.

Group	Plasma donors	Mean value of approximate insulin activity (milliunits in 0.5 ml)	Standard deviation of insulin activity	Mean value of blood-sugar decrease (mg %)
I	24 normal rats fasted 2 hours	14.6	19.3	5
II	14 rats, 2 hours after a single oral ingestion of Carbutamide (300 mg/kg)	83.4	58.2	36
III*	20 rats, treated daily with Carbutamide orally (10 rats: 200 mg/kg; 10 rats: 300 mg/kg) for 3 months, 2 hours after administration (300 mg/kg)	14.8	21.3	8

* Before this period, 10 of these 20 animals had been pretreated for another 6 months with 25 to 100 mg of Carbutamide per kilogram, per day.

All technical papers and comments on them are published in this section. Manuscripts should be typed double-spaced and be submitted in duplicate. In length, they should be limited to the equivalent of 1200 words; this includes the space occupied by illustrative or tabular material, references and notes, and the author(s)' name(s) and affiliation(s). Illustrative material should be limited to one table *or* one figure. All explanatory notes, including acknowledgments and authorization for publication, and literature references are to be numbered consecutively, keyed into the text proper, and placed at the end of the article under the heading "References and Notes." For fuller details see "Suggestions to Contributors" in *Science* 125, 16 (4 Jan. 1957).

liver glycogen level in fasting animals after administration of Carbutamide and Tolbutamide (*3*, *15*), point toward mechanisms that are independent of the stimulating effect of these oral antidiabetics on insulin output.

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Transport of Glucose by the Renal Tubule Cells of Anesthetized Dogs

Under ordinary circumstances the removal of glucose from the urine in the proximal tubules of the kidney is sufficiently complete to prevent the escape into the bladder of any significant fraction of the glucose crossing the glomerular barrier. The glucose moiety absorbed by the proximal tubule is usually considered to combine reversibly with a postulated intracellular carrier and to be returned to the peritubular fluid and thence to the peritubular capillaries and the renal vein. It is generally tacitly assumed that the transport process does not involve breakdown and resynthesis of the six-carbon chain of glucose. It has been suggested as an alternate hypothesis that the transport might involve a three-carbon unit (*1*). Evidence is presented here to substantiate the assumption that the six-carbon chain remains intact during the transport process (*2*).

The procedure is similar to that described in an earlier paper (*3*). Injection of a solution containing the blue dye, T-1824, glucose labeled with carbon-14 in the 1 position, and creatinine is made nearly instantaneously into the renal artery of an anaesthetized dog. Thirty successive samples of renal venous blood are obtained by means of a polyethylene catheter introduced into the left renal vein by way of the inferior vena cava. The concentration of each injected substance, determined in each blood sample, is divided by its concentration in the mass injected. The resultant concentration ratios are plotted as ordinates against sample number or time after injection as abscissas. The results of a representative experiment are shown in Fig. 1 (top).

That the radioactivity in the venous blood samples was derived from glucose rather than from other nonvolatile carbon compounds was established as follows. Paper chromatograms were prepared of desalted perchloric acid filtrates of the blood samples. Glucose was identified by means of aniline phthalate. Radioautograms and strip scanning for radioactivity indicated that glucose was the only substance present that possessed significant radioactivity.

The difference between the glucose and creatinine curves is assumed to represent the glucose absorbed from tubular urine by the proximal tubule cells and delivered to the peritubular capillaries. A necessary corollary of this assumption is that phlorhizin should, by blocking tubular transport of glucose, obliterate the differences between the glucose and creatinine curves. That it does this is shown in Fig. 1 (bottom). The broken line in Fig. 1 (top), relating the differences between the glucose and creatinine ratios, may therefore be taken to represent glucose returned to the circulation by the tubule cell.

Degradation, by a microbiological procedure (*4*), of the glucose in the venous blood samples containing this returned glucose showed that essentially all the recovered radioactivity resided in the 1 position. This absence of randomization establishes that there is no breakdown and resynthesis of the six-carbon chain of glucose in its transport across the tubule cell.

The mean transit time (*5*) from the glomerulus to the peritubular fluid cell border of glucose transported by the tubule cells is calculated as the difference between the mean transit times, from renal artery to catheter tip, of the transported glucose and of the creatinine; the assumption is made that creatinine does not enter these cells from either cell border. The average of the values found in eight experiments is approximately 10 sec. If it is assumed that the mean transit time of glucose from the glomerular barrier to the lumen border of the proximal tubule cells is of the order of 5 sec, then the mean transit time of glucose across the tubular cells is approximately 5 sec. The assignment of the value of 15 μ to the thickness of the cells and the assumption that diffusion is the mechanism of the passage of the complex across the cell permit calculation (*6*) of a value for the diffusion coefficient in the cytoplasm of the postulated glucose-carrier complex. This value is 0.2×10^{-6} cm²/sec. If it is now assumed, as was previously done for *p*-aminohippurate transport (*6*), that

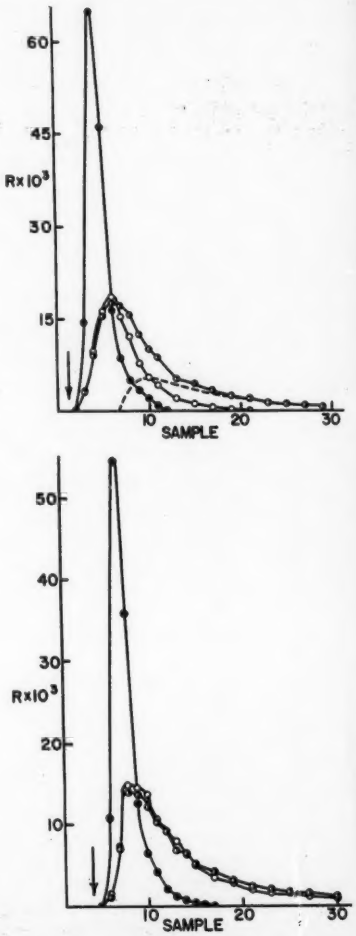

Fig. 1. Ordinates represent concentration of substance in sample divided by concentration in injection mass. Abscissas are the sample number. Filled circles indicate T-1824, open circles creatinine, half-filled circles glucose-1-C^{14}. Arrows denote the moments of injection. (Top) No phlorhizin; broken line indicates glucose returned from tubule urine; collection time, 1.32 sec per sample; (bottom), after phlorhizin; collection time, 1.40 sec per sample.

the viscosity of the cytoplasm is 10 times that of water, the particle weight of the complex is calculated to be of the order of 2000 g/mole. This calculation is presented as the basis for the suggestions that the glucose-carrier complex, if such exists, is not a macromolecule and that the transport does not directly involve organized intracellular particles, such as mitochondria.

In another series of experiments, collection of urine samples was made after injection into the renal artery of glucose uniformly labeled with carbon-14 and of ordinary creatinine; the excretion patterns (6) were then determined. After a load of ordinary glucose to produce glucosuria, the excretion patterns of C^{14}-labeled glucose and of creatinine were symmetrical. No displacement of the patterns, such as has been found with urea relative to creatinine (7), was noted. This finding suggests that glucose entering the tubule cells does not return to the lumen. After the administration of phlorhizin, the excretion patterns of C^{14}-labeled glucose and of creatinine were essentially identical. It is inferred from these findings that the combination of glucose with the postulated intracellular carrier occurs at the cell barrier rather than within the cell. That glucose may enter the cells from the peritubular fluid side is suggested by the finding, in most experiments of the type illustrated in Fig. 1, of glucose concentration ratios somewhat less than the creatinine concentration ratios in the samples at or preceding the maxima. No marked change in this relationship was noted after phlorhizin.

These findings form the basis for the following tentative conclusions. (i) Glucose is transported by the renal tubule cells without breakdown and resynthesis of the six-carbon chain. (ii) The transport system is of the membrane carrier rather than of the cytoplasm carrier variety. (iii) The postulated glucose-carrier complex is not a macromolecule.

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22 January 1957

Protection of Sulfhydryl Groups against Ionizing Radiation

Sulfhydryl compounds have long been known to be among the most radiosensitive of all organic compounds. A number of them, such as cysteine, glutathione, cysteamine (β-mercapto ethylamine) and 2,3-dimercapto 1-propanol (BAL) have been used as protective agents against the action of ionizing radiation. Their protective action was assumed to be owing to their ability to act as "free radical acceptors"—that is, to compete with other components of the system for the free OH, H, or HO_2 radicals formed as primary products of radiolysis of water.

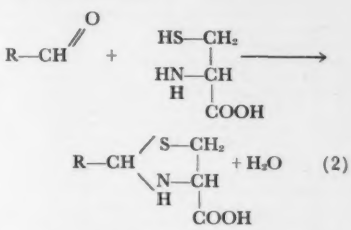
Recently, however, Eldjarn *et al.* (1), using "labeled" sulfur components, demonstrated that the protective action of cysteamine and cystamine ($HS—CH_2—CH_2NH_2$ and $NH_2 \cdot CH_2—CH_2—S—S—CH_2—CH_2 \cdot NH_2$) was due not so much to their ability to scavenge free radicals, but rather to a specific chemical reaction of cystamine with free sulfhydryl groups of the protein molecules. By this reaction, cystamine forms a disulfide linkage according to the scheme

$$\text{Protein—S—H} + \text{R—S*—S*—R} \rightarrow \text{protein—S—S*—R} + \text{H—S*—R} \quad (1)$$

where R—S*—S*—R represents the (labeled) cystamine and H—S*—R represents the resulting cysteamine. The resulting disulfide linkage appears to be much more resistant to the action of ionizing radiation than the "unprotected" sulfhydryl group, thus accounting for the effectiveness of these compounds as protective agents. The blocking of the sulfhydryl groups is temporary, and they are eventually restored by normal biological processes.

In the course of investigations of the development of odors on irradiation of food, we became interested in the formation of hydrogen sulfide and mercaptans as contributors to the odor problem, and consequently in methods of prevention of their formation. Because of the extreme radiosensitivity of the sulfur compounds involved, particularly cysteine and glutathione, effective reduction of the hydrogen sulfide formation by addition of free radical acceptors such as ascorbic acid did not appear to be promising.

The work of Eldjarn pointed out another approach—namely, masking these sulfhydryl groups by specific chemical reactions, rather than protecting them by competing reactions. Considerable work had been done in this direction. Schubert (2) and Vuataz (3) found that a number of carbonyl compounds were capable of reacting with sulfhydryl compounds even in dilute aqueous solutions, forming mercaptals, and reported that some of these no longer showed the characteristic sulfhydryl reactions, such as the purple nitroprusside color. The situation seemed to be particularly favorable in the presence of α-amino groups (such as in cysteine), since stable thiazole rings could be formed:



A number of aldehydes, dialdehydes, keto aldehydes, and keto acids were tried as additives, using approximately 100 percent excess. A nitroprusside test was made first; the mixture was then subjected to the action of atomic hydrogen and γ-rays. The techniques used for the production of hydrogen atoms as well as for treatment with γ-rays from a Co^{60} source have been described elsewhere (4). The best protection of cysteine against the action of atomic hydrogen was provided by glyoxal, formaldehyde, pyruvic acid, pyruvic aldehyde diacetyl, and glyceraldehyde, which reduced the amount of H_2S formed to 10 to 15 percent of that formed in unprotected solutions. By contrast, ascorbic acid used in tenfold excess reduced the amount of H_2S only to about one-half. Glutathione was protected best by glyoxal, pyruvic acid, and formaldehyde.

The protection against γ-rays, used at a level of 5×10^6 rep, is even more favorable. No measurable amount of H_2S was formed from cysteine solutions at *p*H 7 when either glyoxal or pyruvic acid was used as an additive in 100 percent excess. This compares favorably with ascorbic acid, which afforded only a 30 percent reduction of H_2S formation. With glutathione at *p*H 7, glyoxal (in 100 percent excess) prevented the formation of H_2S almost completely, pyruvic acid provided a 65 percent reduction; ascorbic acid used for comparison resulted in a 50 percent reduction of H_2S formation. A number of aldoses were tried but found to be ineffective, with the exception of glyceraldehyde. This is consistent with the assumption that sugars containing four or more carbons form cyclic hemiacetals and thus do not possess a reactive aldehyde group.

These results indicate that the masking of radiosensitive groups by specific chemical reactions may be a more effective way of reducing certain effects of ionizing radiation than the addition of free radical acceptors (*5*).

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Effect of Multiple Recrystallization on Derivatives of Mixtures of D- and L-Alanine

Among the problems encountered in tracer studies with biological systems is the difficulty of isolating a compound that is present in minute amounts. To reduce the difficulty of this problem, it is a common practice to add as carrier the non-labeled material sought and then to proceed with the isolation. As a matter of convenience, the DL racemate is sometimes added, although the compound sought may be solely of the D or L configuration. A question arises about the degree of significance of the isomeric nature of the carrier. This is of particular importance if the radioactivity of the isolated material is to be interpreted as representative of the activity of the compound as it exists in the biological preparation.

In the same regard, it is often desirable to determine the amount of the compound in the system. One manner in which this is done involves establishment of the isotope dilution. Again, the significance, if any, of the isomeric form may become an important consideration. This is especially true if the compound is to be isolated as a derivative. It was from interest in the latter case that the present investigation (*1*), which employed a particular system involving the isolation of alanine as the azobenzene sulfonate derivative, was initiated.

Table 1. Radioactivity (count/min) of alanine azobenzene sulfonate.

No. of recrystallization	Source of derivative		
	Parent DL-alanine	Diluted DL-alanine	1/3 D- to L-alanine
1	113	55	52
2	112	56	49
3	110	57	45
4	109	56	42
6	112	56	39

The magnitude of changes in activity during multiple recrystallization of derivatives of alanine having equal activity but differing in the ratios of the D to L isomers has been investigated. Other derivatives prepared from alanine of the same and of unequal amounts of D and L configuration have also been studied.

Two mixtures of alanine were prepared from a parent source of racemic alanine-1-C^{14}. The first was prepared by diluting the radioactive material with an equal amount of DL-alanine. The second mixture contained equal amounts of the radioactive racemate and L-alanine. The mixtures were dissolved in water to insure complete mixing and were then precipitated by the addition of ethanol. In this manner, two alanine mixtures were obtained with equal radioactivity contributed from the D and L isomers, but with different total proportions of the isomers. The first mixture was racemic, while the second contained the D and L isomers in a ratio of 1/3. The alanine salt of azobenzene-*p*-sulfonic acid (*2*) was prepared from each of these mixtures as well as from the parent racemic alanine. The salts were recrystallized once from water, dried, and assayed for radioactivity. Each of the compounds was subsequently recrystallized several times from water and counted following each recrystallization.

The radioactivity was measured on pressed solid mounts of the derivative plated at infinite thickness. Recrystallized samples were mounted in the same aluminum planchet to maintain identical counting-surface area. All counts were made with a thin end-window Geiger-Müller tube. The values reported are expressed as total counts per minute for the sample less background. Since the same derivatives are compared, these values are both proportionate to the activity per milligram and per millimole of derivative. The results of these determinations are shown in Table 1. The activities of the salts of the parent and diluted racemate did not change, while the activity of the 1/3 D- to L-alanine derivative steadily decreased. Based on the mean activity for the salt of the parent alanine, the salt of the racemate after six recrystallizations had 100 percent of the theoretical activity, while the activity of the 1/3 D to L mixture had dropped to 70 percent.

Another alanine mixture was prepared in the manner already described in which the D- and L-isomers were present in a ratio of 2/3, respectively. From this mixture, the phenyl isocyanate (*3*) and *p*-toluenesulfonyl (*4*) derivatives were prepared. After five recrystallizations, neither of these derivatives showed a change in radioactivity. The fact that no apparent shift in activity was observed may be dependent on the nature of the derivatives or the concentrations of the two isomers, which in this case were more nearly equal.

As a final experiment, two alanine mixtures were prepared from a source of racemic alanine-1-C^{14} in such a manner that one contained the isomers in a ratio of 1/3 D to L and the other 1/3 L to D. The mixtures had equal amounts of C^{14} in each isomeric form. Again the azobenzene-*p*-sulfonic acid salt was made from each of the mixtures and recrystallized. In Fig. 1 are shown the changes in radioactivity with subsequent crystallizations. As a control, the same derivative was prepared from a DL-alanine-1-C^{14} source and was likewise subjected to recrystallization. The data are included in Fig. 1. The radioactivity of the 1/3 D to L and the 1/3 L to D derivatives showed a consistent and similar decrease. The results with the alanine azobenzene sulfonates may be explained in each case by an enrichment of the isomer originally present in the larger amount.

The isomeric nature of the carrier appears to be worthy of consideration in the preparation of a derivative from an optically active compound. The degree of importance varies with the derivatives of choice, the number of crystallizations, and the ratio of the D and L isomers. In many situations, analytic results will not be affected to a significant degree by excessive crystallization. However, the im-

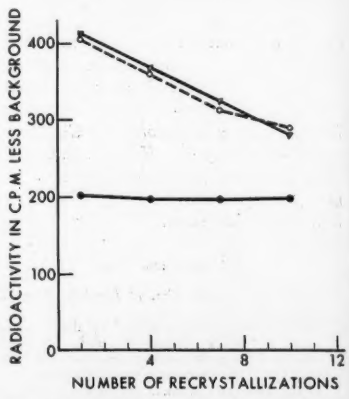

Fig. 1. Effect of successive recrystallization on the radioactivity of alanine azobenzene sulfonates; △, derivative prepared from 1/3 D- to L-alanine; ○, derivative from 1/3 L- to D-alanine; ●, derivative from a racemic mixture.

portance is intensified in certain instances and should be considered in any situation where multiple recrystallization is to be encountered.

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Changes of Thixotropic Behavior in Actomyosin Solutions Induced by Cardiac Glycosides

Actomyosin solutions are thixotropic, which literally means that they "change by touching." An internal structure formed by the fibrous protein molecules is partially broken by agitation of the fluid, and, for example, the viscosity is accordingly diminished. As long as the flow remains constant, the structure will not reform. As soon as flow stops, thixotropic structure is built up again.

For measuring changes in viscosity, the thixotropy has to be kept at a steady state. In making these measurements with an Ostwald viscosimeter, we found that numerous active and inactive cardiac glycosides reduce the viscosity of actomyosin solutions parallel to the degree of biological fixation on heart muscle. The binding of some glycosides to actomyosin was proved by ultrafiltration and determination of the dissociation constants. One receptor group per molecule of actomyosin (molecular weight taken as 10^6) was found, probably belonging to myosin (*1*).

The thixotropy of actomyosin that had been extracted from rabbit skeletal muscle was studied in a rotational viscosimeter at 0°C. Eighteen milliliters of protein solution (3 mg/ml in Weber-Edsall fluid with barbiturate buffer) was placed in a narrow cylindrical slit in which another cylinder was rotated with constant speed. The breaking force on the cylinder exerted by the viscous solution was counteracted by a spring and was measured on a dial. It was proportional to the viscosity of the fluid.

We measured the coefficient of "thixotropic breakdown with time" (*2*):

$$B = \frac{U_1 - U_2}{\ln \frac{t_2}{t_1}}$$

where U_1 is the viscosity at time t_1 and U_2 is the viscosity at time t_2. The times t_1 and t_2 were 1 and 10 minutes, respectively. Both the coefficient for actomyosin (B_{AM}) and for actomyosin of the same concentration with 10^{-6} *M* glycoside (B_{AMG}), were determined. No alcohol was used to increase solubilities, for we found that even traces of alcohol caused fundamental changes in actomyosin. The difference in thixotropy ($B_{AM} - B_{AMG}$) was then compared with the biological activity (see Fig. 1). Potency is expressed as reciprocal of lethal Hatcher dose (moles per kilogram) determined in cats by W. R. Schalch of Sandoz AG. Basel. The probability that Δ-thixotropy ($B_{AM} - B_{AMG}$) is significant (< 0.02 to 0.05) was computed from the variances of the determinations of $B_{AM} - B_{AMG}$ using the *t* distribution.

There exists an interesting correlation between these two properties. Cardioactive glycosides diminish the thixotropy, whereas biologically inactive glycosides (potency = 0) augment it. Activities of lanataglycosides are approximately proportional to the decrease of thixotropy. In three cases (open bars in Fig. 1: digitoxin, acetyldigitoxin α, and acetyldigoxin α) in which the ion concentration in the solution was diminished by adding the glycosides in water instead of buffer solution, the effect was larger than was expected from the biological activities. This may be connected with the poor water solubility of these three glycosides, or else with the decrease of the ion concentration. A change in the active ion concentration or some other charge phenomenon along the actomyosin fiber may be responsible for the observed effect. Preliminary studies on the dialysis of actomyosin in 0.6*M* K solution have shown the concentration of free potassium ions to be diminished by adding 10^{-6} *M* glycosides (lanatosid A, B, C, scillaren A, cymarin, and strophanthin) but not by the inactive glycosides hexahydroscillaren A and allocymarin.

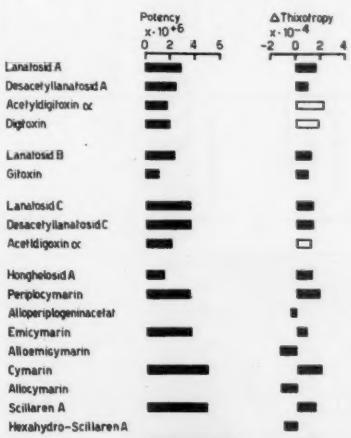

Fig. 1. Comparison of difference in thixotropy ($B_{AM} - B_{AMG}$) with biological activity.

It is therefore possible that there exists a direct mode of action of cardiac glycosides on actomyosin within the cell and not only in the cell membrane phase, as was suggested by previous workers (*3*).

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7 February 1957

Withdrawal Hyperexcitability Following Chronic Administration of Meprobamate to Mice

Because of known side effects and potential "behavioral" toxicity, concern over the indiscriminate use of the so-called "tranquilizing agents" is readily justified. However, the added possibility that these drugs might also possess addiction liability has been little, if at all, explored. Recently, Lemere (*1*) reported that one patient who took 6.4 g of meprobamate (Equanil, Miltown) daily for 30 days exhibited a grand mal convulsion 10 hours after therapy was discontinued. In view of this report, the effects of the chronic administration of this agent and its abrupt withdrawal on the excitability of the central nervous system of mice, by use of the experimental design developed by McQuarrie and Fingl (*2*), were studied.

Since this investigation (*3*) was planned merely to determine whether tolerance develops during the chronic administration of meprobamate and whether abrupt withdrawal is followed by increased excitability of the central nervous system, only high dose levels were employed. This choice of dosage was justified also on the bases that large amounts are taken by patients who abuse drugs and that excessive quantities are usually necessary to demonstrate physical dependence on ethanol and barbiturates in man (*4*, *5*). It must be emphasized that final assessment of the addiction liability of any drug must be based on quantitative comparison of the dosage schedules that induce withdrawal phenomena with those that are required to obtain therapeutic results.

Male albino mice (Carworth Farms, CF #1 strain, 25 to 35 g in weight) were

randomly divided into two groups of 50 animals each. Meprobamate (*6*) was administered orally to one group either as a 2- or 3-percent suspension in 6-percent acacia solution in a total daily dose of 1200 mg/kg (200 mg/kg at 8 A.M., 12 noon, 4 P.M., and 8 P.M., and 400 mg/kg at 12 midnight) for 6 days. Because of the development of tolerance, following the 8 A.M. treatment on day 7, each dose was increased by 50 percent to make a total daily dose of 1800 mg/kg; this higher dose level was continued for 10 days, except as indicated in the legend to Fig. 1. The other group served as a control and was given the requisite volume of 6-percent acacia solution. Low-frequency electroshock seizure threshold was determined for both groups at the times indicated in the legend to Fig. 1. Seizures were induced by means of a Grass stimulator (model S4B). The stimulus parameters employed were the same as those previously described (*7*)—namely, unidirectional pulses of 0.2-msec duration delivered for 3 seconds at a frequency of 6 pulses per second. Mice were shocked at various voltages by the staircase procedure (*8*), and the voltage required to evoke convulsions in 50 percent of each group was determined; the 95-percent confidence limits were calculated by the method of Litchfield and Wilcoxon (*9*). Results are presented as the threshold ratio (threshold of drug group/threshold of control group). In a separate series of experiments, 80 mice were divided into two equal groups. One group was given orally 300 mg/kg of meprobamate, and the other group the requisite volume of 6-percent acacia solution; the seizure threshold of each group was determined 30 minutes after drug administration. This procedure was repeated at intervals of 3 or 4 days in the same groups of mice until the seizure threshold was established 1, 2, 3, and 4 hours after drug administration.

As illustrated in Fig. 1, tolerance develops to the threshold-raising effect of meprobamate. For example, the administration of 300 mg/kg of meprobamate to nontolerant animals increased the threshold more than tenfold (see small inset in Fig. 1), whereas, after treatment for 6 days with 1200 mg/kg day and then for 10 days with 1800 mg/kg day, this same dose of drug increased the threshold only 2.5-fold.

Figure 1 also illustrates that, 4 hours after the 8 A.M. dose on day 12 and 4 hours after drug withdrawal on day 17 (see *B* and *E*, Fig. 1), the seizure threshold in meprobamate-treated mice was only approximately 0.8 that of control animals. Such hyperexcitability (but of lesser degree) was also observed 8 hours after the double midnight dose on day 13 and 8 hours after the 8 A.M. dose on day 14 (see *C* and *D*, Fig. 1). Since seizure threshold is not reduced 4 hours after the single administration of this same dose of meprobamate to nontolerant animals (see small inset in figure), the withdrawal hyperexcitability must be attributed to the chronic administration of this agent.

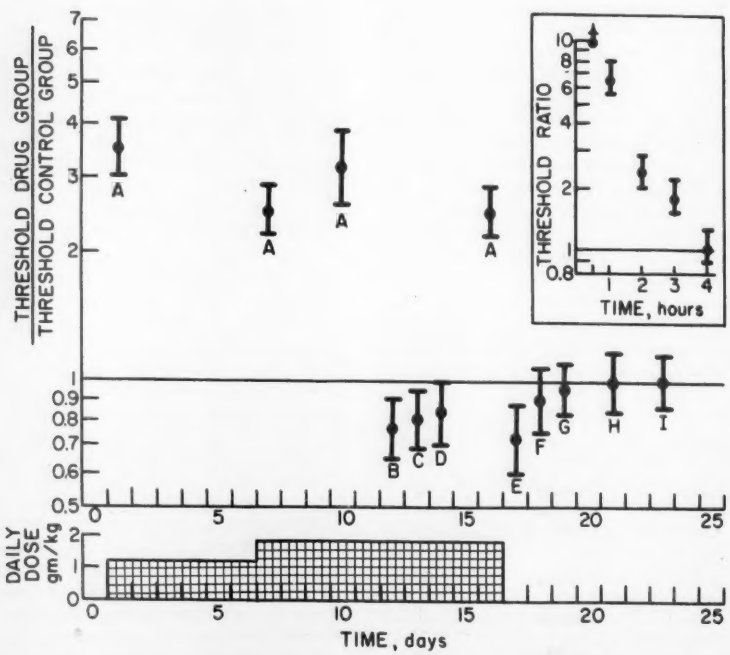

Fig. 1. Effects of chronic administration of meprobamate on threshold for low-frequency electroshock seizures in mice. Time in days is indicated on the abscissa. Seizure threshold ratio (threshold of drug group/threshold of control group) is shown on the upper ordinate, and total daily dose administered is shown on the lower ordinate. Vertical bracketed lines indicates 95-percent confidence limits. *A*, *B*, and *D* indicate the ratio at ½, 4, and 8 hours, respectively, after an 8 A.M. dose; *C* indicates the ratio 8 hours after the double midnight dose; *E*, *F*, *G*, *H*, and *I* indicate the ratio at 4, 28, 52, 100, and 148 hours, respectively, after the final dose of the drug. The inset in the upper right-hand corner illustrates the duration (in hours) of the effect of a single dose of meprobamate (300 mg/kg) on seizure threshold.

Hyperexcitability in mice following the chronic administration of either ethanol or phenobarbital is usually not present 24 hours after drug withdrawal, is maximal on day 2 or 3, and declines progressively over the next 2 to 4 days. In the studies reported here, hyperexcitability in mice following chronic administration of meprobamate is detectable 4 and 8 hours after drug withdrawal and subsides within 28 hours. At the clinical level, tremors and nervousness may be experienced during the first day of abstinence from either ethanol or barbiturates, but the most severe withdrawal symptoms appear later, spontaneous convulsions usually occurring between the second and the fifth day after ingestion of the drug has been stopped (*4*, *5*). In contrast, hyperexcitability climaxed by a grand mal convulsion has been noted 10 hours after meprobamate withdrawal (*1*). Thus, the time course of hypersusceptibility to induced seizures following cessation of chronic administration of either ethanol, barbiturates, or meprobamate in mice appears to parallel that of withdrawal hyperexcitability in man.

The abstinence syndrome which occurs in man following the chronic abuse of barbiturates is characterized by hyperexcitability, which may progress to convulsions, and by psychosis. This withdrawal syndrome is qualitatively similar to that which occurs upon withdrawal of various other central nervous system depressants, including ethanol, chloral hydrate, and paraldehyde (*4*, *10*). However, the relative prominence of these major withdrawal symptoms, and particularly the time course, vary with the addicting drug. Clinical observations such as those of Lemere (*1*) suggest that meprobamate should be added to the list of drugs that cause withdrawal syndromes, and the experiments in mice described herein support this view. The meprobamate abstinence syndrome differs from the others by its more rapid development and briefer duration. Whether psychosis can occur as a feature of the meprobamate withdrawal syndrome remains to be explored. Like-

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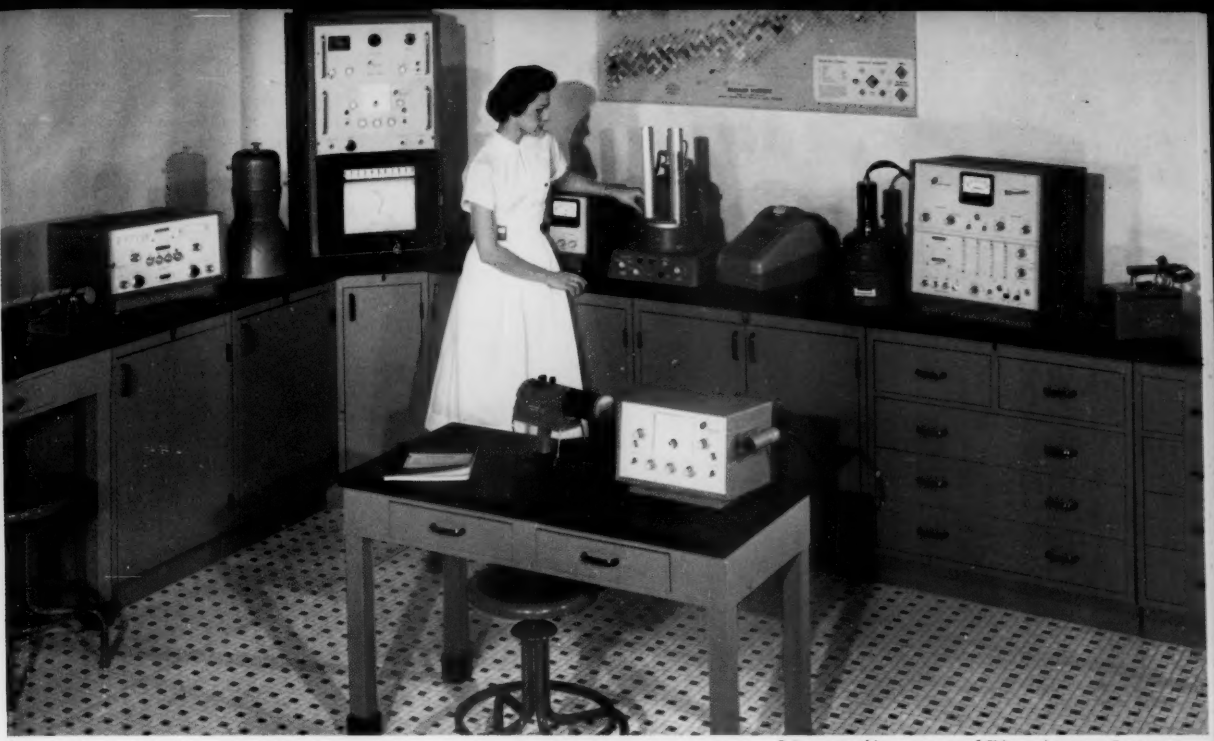

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wise, the minimal dosage schedules which induce withdrawal phenomena have yet to be established.

Two important clinical implications merit brief mention. First, the qualitative similarity of the meprobamate and the barbiturate abstinence syndromes implies that precautions should be taken to minimize both the development of physical dependence on meprobamate and the severity of the withdrawal syndrome; such precautions as those currently used in the case of barbiturates could be expected to be effective. In particular, following a period of chronic administration of large doses of the drug, medication should never be stopped abruptly. The second implication is that demonstration of physical dependence and an abstinence syndrome following abuse of meprobamate suggests that all members of the new classes of tranquilizing agents should be held suspect until definitely proved to be devoid of such undesirable properties.

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22 January 1957

Enlargement of Avian Eye by Subjecting Chicks to Continuous Incandescent Illumination

During studies on the effect of different durations of diurnal artificial illumination on the growth of chicks, it was observed that the eyes of chicks subjected to continuous light appeared to be flattened. This condition was manifested by reduced depth of the anterior chamber and the apposition of the periphery of the iris to the cornea.

Because of these observations, the eyeballs of chicks from two different lighting treatments were subjected to certain measurements. Eight chicks that were exposed to continuous incandescent illumination and eight chicks that received such light for 12 hours daily provided the material for the study. Each pen, from which all natural light was excluded, received artificial light from a 60-watt, frosted incandescent lamp with a light intensity of 2 to 3 ft-ca measured at the bird height. The chicks were 6 weeks of age when they were sacrificed, and they had been on the two different light treatments since the day after hatching.

The average weight of eyeballs removed from chicks that had received continuous light was about 38 percent greater than the weight of eyeballs of chicks that had received only 12 hours of artificial light each day (Table 1). When the weight of the eyeballs is expressed as a percentage of body weight, there is still a large difference between the two treatments. Thus the data show that an enlargement of the eyeballs of chicks was produced by continuous artificial light.

It was of interest to determine whether the increased size of the eyeballs was brought about largely by an increase in tissue water content or by an increase in both water and tissue dry matter. When fluid was drawn from the posterior chamber of the eye by a hypodermic syringe, about twice as much fluid could be extracted from the eyeballs of chicks that had been subjected to continuous light (0.80 ml per eye) as could be extracted from the eyeballs of chicks that had been subjected to 12 hours of diurnal light (0.45 ml per eye). When the dried weight of the eyeballs is expressed as a percentage of the live body weight, there is only a slight difference between the two treatments. These results show that the increased size of the eyeballs of chicks that received continuous light was caused primarily by an increased accumulation of fluid.

It was found that the average diameter of eyeballs enucleated from chicks that received continuous light was 2.4 mm larger than that of eyeballs from chicks that had not received continuous light. Although average depth was also slightly increased, it appeared that the major change was in the diameter of the eyeballs.

A peculiar enlargement of eyeballs in chicks caused by feeding them a high level of glycine was reported by Groschke *et al.* (*1*). In these studies, the eyes were greatly enlarged by the addition of 8 percent free glycine to a purified diet. When a similar amount of glycine was added in the peptide form, no such enlargement was observed.

The data presented in this report (*2*) indicate that investigations on the effect of continuous illumination on the eye might well be expanded to determine the mechanism of the development of the abnormality. A study of the relationship of this light-induced abnormality to that of eye abnormalities in other species, including man, would be of interest.

Table 1. Effect of length of diurnal incandescent illumination period on eyes of chicks.

Item	Daily illumination period	
	24 hours	12 hours
No. of chicks	8	8
Av. body weight at 6 wk (g)	760	733
Av. weight of eyeballs (g)	4.83	3.50
Av. weight of dried eyeballs (g)	0.515	0.465
Av. diameter of eyeball (mm)	17.6	15.2
Av. depth of eyeball (mm)	12.9	12.1

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28 January 1957

Effects of Embryonic Age on Potency in Tissue Culture of Embryonic Nucleoprotein Fractions

In the preparation of various biological growth media, and especially those for tissue culture, it is customary to use whole embryo extract as a source of growth-promoting factors (*1*). The choice of age of chick embryo used for making the extract is commonly one of convenience, usually embryos of 8 to 11 days (*2*). However, Gaillard (*3*) and Fowler (*4*) found that growth of chick heart fibroblasts in plasma culture was stimulated more by saline extracts of 14- to 18-day chick embryos than by similar extracts of 8- to 11-day embryos.

Recently a streptomycin-precipitation procedure was developed using 12-day chick embryos for isolation of the high-molecular-weight growth factors from whole-embryo extract (*5*). It seemed of interest to determine whether this active nucleoprotein fraction (NPF) would show a similar increase in potency or specific activity—that is, biological activity at the same concentration with in-

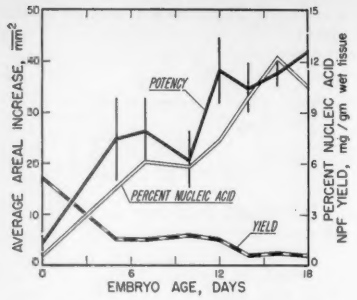

Fig. 1. Changes in yield, potency, and nucleic acid content of the nucleoprotein fraction (NPF) with age of embryonic source tissue.

crease in age of the embryo. It was further hoped that the study might disclose a source of the nucleoprotein fraction with higher yield and greater potency than 12-day embryos (*6*).

Using this streptomycin procedure, nucleoprotein fractions were prepared from nonfertile egg yolk and chick embryos that were 5, 7, 10, 12, 14, 16, and 18 days old. The egg white was devoid of streptomycin-precipitable material of appreciable quantity. The tissues were homogenized in borate with the aid of a Waring Blendor or Teflon-glass homogenizer. Streptomycin was used to precipitate the nucleoproteins from the borate extracts. Suspension of the nucleoprotein fraction in 1*M* NaCl was followed by dialysis against 1*M* NaCl and clarification in the ultracentrifuge. The clear solution was dialyzed against Gey's solution and finally was clarified in the ultracentrifuge. Dry weights and ultraviolet absorption spectra were obtained from aliquots of the clear fractions prior to culturing.

Tissue-culture assays were made using standard techniques (*7*). Fresh explants of 10- to 14-day chick embryo heart were singly cultivated in D-3.5 Carrel flasks at 37°C for a 7-day period. The basal assay medium consisted of a chicken plasma clot in which an explant (1 mm³) was embedded, with a fluid supernatant of 20 percent horse serum and 80 percent Gey's solution. The nucleoprotein fractions were incorporated in the Gey's solution at the appropriate concentrations. Antibiotics were routinely incorporated into the media. Each test fraction was assayed in a series of six Carrel flasks, and each group of tests included a background control set of six flasks. Supernatant fluids were changed at 4 days, and cultures were traced and terminated at 7 days. Areal increases over and above the control values at 7 days were determined, and statistics (mean value and standard error) were calculated for each series of six cultures.

The average areal increase for the nucleoprotein fractions at 0.4 mg/ml in culture is shown as a function of embryonic age in Fig. 1. The points represent the averages of two extraction series. A general increase of areal outgrowth with increasing embryonic age is to be noted. The differences become significant ($P = 0.02$) when the 10-day nucleoprotein fraction is compared with the 16- or 18-day fraction.

The yields of nucleoprotein fraction per gram of wet starting tissue were calculated and plotted in Fig. 1. The steady decrease in yield with age may be partly accounted for by the difficulties of homogenization and extraction of the older tissues.

Ultraviolet absorption spectra of all the nucleoprotein fractions were similar to the spectrum of the 12-day fraction already published (*5*) with the exception of that of the egg yolk fraction. The latter had a maximum at 280 mμ, indicating a preponderance of proteins and a relatively small quantity of nucleic acids.

The content of total nucleic acids as percentage of dry weight was determined on 5 percent perchloric acid extracts (*8*) by comparing their ultraviolet absorption at 260 mμ with that of Schwartz ribonucleic acid standards. The results are shown in Fig. 1. A steady increase with age of total nucleic acids is to be noted. The nucleic acids are largely ribonucleic acid; previous analyses on the 12-day chick embryo nucleoprotein fraction disclosed that deoxyribonucleic acid accounted for less than one-tenth of the total nucleic acids (*5*).

The results indicate that the high-molecular-weight growth factors are present at all ages and do indeed contribute to the increased potency of whole extracts of older embryos as found by Gaillard (*3*) and Fowler (*4*). However, the decrease in yield of nucleoprotein fraction with age would indicate that the 12-day embryo is the best and most productive source. The parallel increase of nucleic acid and potency of the nucleoprotein fractions may be fortuitous and may reflect only an increase in quantity of nucleic acids in the enlarging embryo since the streptomycin precipitation carries down free nucleic acids as well as nucleoproteins (*9*). Other investigations on adult tissue nucleoproteins (*10*), as well as on embryonic nucleic acids (*5, 11*), indicate that nucleic acids as such are inert in this type of tissue culture. Preliminary experiments indicate that the protein portion of the nucleoprotein fraction is active (*12*). An alternative explanation for the parallel increase of potency and nucleic acid content is possible since unpublished experiments on the stabilization of the nucleoprotein fraction suggest that an increase in nucleic acid content may promote increased protection or stabilization of the active nucleoprotein fraction during isolation procedures. The role of nucleic acids as stabilizers during isolation is being actively investigated.

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8 February 1957

Effect of Zymosan on Bacteriophage Clearance

Soon after the discovery of bacteriophage, it became evident that the initial enthusiasm over possible therapeutic application of phage was unwarranted. Among the reasons propounded for the relative lack of success were included the development of resistant bacterial strains, actual deleterious effects due to toxic cleavage products in phage lysates (*1*), failure of phage to reach the focus of infection or to lyse susceptible bacteria *in vivo*, and the inactivation of phage by host defense mechanisms (*2*).

Several investigators (*3*) have reported that human serum, purulent exudates, and other body fluids inactivate phage. The discovery by Pillemer *et al.* (*4*) of the properdin system, a natural defense mechanism effective against a variety of bacteria and animal viruses, suggested to us that this normal serum constituent may be responsible in part for the inactivation of bacterial viruses *in vivo*. Therefore, experiments were initiated to determine whether bacterial viruses are inactivated by the properdin system. While these studies were in progress, Van Vunakis and her associates (*5*) reported the *in vitro* inactivation of *Escherichia coli* phage by the properdin system.

Preliminary experiments in our laboratory revealed that approximately 60-percent inactivation resulted during incubation of staphylococcus phage (typing strain No. 53) with fresh normal rabbit serum at 37°C for 1 hour. Loss

of phage activity was insignificant in serum inactivated by heat (56°C for ½ hour) or treated with zymosan (*6, 7*) at 17°C (two times with 2 mg of zymosan per milliliter). This degree of inactivation is comparable to the results obtained by Van Vunakis *et al.* (*5*). These data suggested a series of *in vivo* experiments, herein reported, to determine the effect of zymosan on phage clearance in the blood stream of experimental animals.

Initially rats were used, but the difficulties inherent in repeated blood sampling caused us to select rabbits as more suitable experimental animals, although these animals have considerably less demonstrable properdin (*7*). The experimental animals received (usually intracardially) approximately 100 mg of zymosan per kilogram of body weight. Control animals received saline injections in lieu of zymosan. Four hours later, each animal was injected with 1×10^9 staphylococcal phage 53 via the marginal ear vein. At intervals, the animals were bled from the heart with a 21-gage needle and tuberculin syringe, and the phage content of the blood sample was immediately assayed by dilution plating on the host bacterium (PS 53).

The combined results of several series of experiments are illustrated in Figure 1. In animals pretreated with zymosan, plaque counts at any time of assay usually range from three to more than tenfold higher than their untreated counterparts. The initial blood samples, with one exception, contained considerably less phage than could be expected on the basis of blood volume dilution (approximately 100-fold, with blood volume considered as 5 percent of body weight, *8*). This observation is in accord with a previous report (*9*) of a 2500-fold reduction of phage in the blood of rats 5 minutes after injection. One must conclude, therefore, that there is an active removal of bacteriophage which is measurable 2.5 minutes after administration in both control and zymosan-treated animals. It is also apparent that pretreatment with zymosan reduces the efficiency of the mechanism(s) responsible for phage clearance.

A decreased rate of phage clearance was also observed when a sublethal dose of *E. coli* endotoxin preparation (*10*) was administered to rabbits. Similar endotoxin preparations have been demonstrated to have marked effects on the properdin system (*11*), but it must be remembered that such preparations have a variety of other effects on experimental animals.

We have been unable to assay properdin according to the methods published by the Western Reserve group (*7*) but preliminary observations suggest that the bactericidal activity against *Shigella dysenteriae* of serum from zymosan-treated animals is less than that of control serums. Although elevated levels of properdin have been reported to follow administration of zymosan (*12*), we have been unable to demonstrate this "rebound" effect with phage clearance when rabbits were challenged with phage 4 to 5 days after zymosan treatment. However, it is possible that only a threshold level of properdin is required for maximal blood clearance of phage, and increases in properdin above this level may have no additional effect on this experimental system.

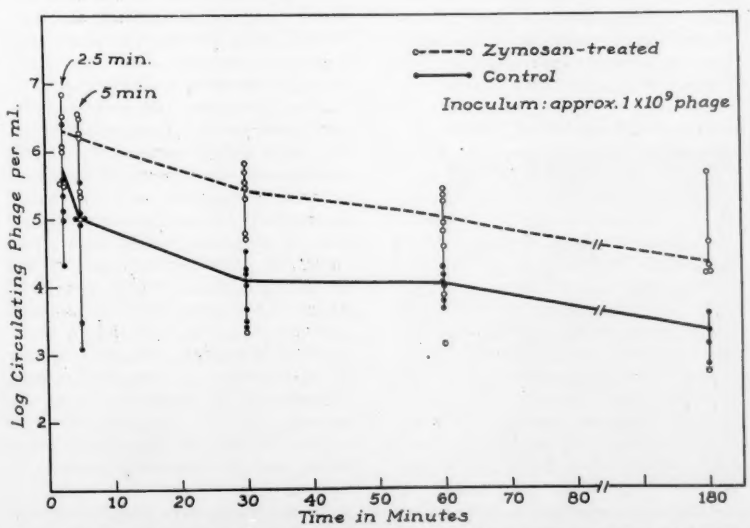

Fig. 1. Bacteriophage clearance in zymosan-treated rabbits. Curves represent arithmetic means of values derived from several experiments. Experimental rabbits received zymosan (100 mg/kg) 4 hours prior to phage inoculation.

The reported observations constitute presumptive evidence that the properdin system may be involved in the inactivation of bacteriophage *in vivo*, but additional confirmatory information is desirable.

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28 January 1957

Pyridine-2-Aldoxime Methiodide and Poisoning by Anticholinesterases

This laboratory has reported (*1*) that certain compounds containing quaternary ammonium groups are capable of enhancing the rate at which the gastrocnemius-soleus-tibialis anticus muscle group of the cat recovers responsiveness to slow (one shock per 2 seconds) stimulation of the sciatic nerve, following weakening or abolition of this response by intravenous injection of a large dose (200 μg/kg) of the potent cholinesterase inhibitor, isopropyl methyl phosphonofluoridate (sarin). In continuation of this work, we have examined the effects of some of the same quaternary compounds on the maintenance of tension in cats poisoned by intravenous injection of about 12 LD_{50} of either sarin or ethylphosphoro dimethyl amidocyanidate (tabun), by the gastrocnemius-soleus-tibialis anticus muscle group stimulated indirectly by just supramaximal stimuli of tetanizing frequency (40 per second). The ability to maintain a tetanus with indirect electric stimulation has been shown (*2*) to be more sensitive to decrease by anticholinesterase compounds than that to produce single twitches.

Oxamide derivatives [N,N′-bis(N-dipropyl, N-2-chlorobenzyl ammonoethyl) oxamide dichloride (WIN 12306), for

example] which promote recovery of the anticholinesterase-inhibited twitch (*1*) had no important effect on recovery of the tetanic response after poisoning with tabun (Fig. 1) or sarin. Another quaternary compound that was found (*1*) to speed recovery of the twitch response, N-benzyl atropinium chloride, had some efficacy in enhancing recovery of the tetanic response after sarin administration (Fig. 1). Figure 1 shows, however, that even with N-benzyl atropinium chloride, the tetanic response did not become reasonably normal within the observation period of 2 hours after the poisoning.

Our attention turned then to oximes, and especially to pyridine-2-aldoxime methiodide (2-PAM). This compound has been reported to be quite active *in vitro* in reactivating cholinesterase inhibited by TEPP, DFP, or sarin (*3*), in overcoming neuromuscular block induced by the same cholinesterase inhibitors in the isolated phrenic-diaphragm preparation of the rat (*4*), and in preventing mortality in mice that have been poisoned with paraoxon (*5*). Other oximes were found (*4*) to be effective *in vivo* in overcoming anticholinesterase-induced neuromuscular block in the gracilis muscle of the rat and in the tibialis of the cat.

Intravenous injection of 5 mg of 2-PAM per kilogram after intravenous administration of about 12 LD_{50} of either sarin or tabun produced comparatively rapid and complete recovery of the tetanic response (Fig. 1). This recovery

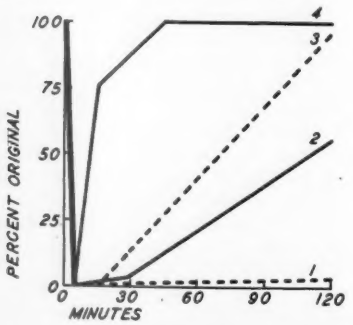

Fig. 1. Effects of various treatments on the recovery, by the gastrocnemius-soleus-tibialis anticus muscle group of the cat, of ability to maintain a tetanus for 30 seconds of indirect electric stimulation with just supramaximal square-ware stimuli. Atropine (0.5 mg/kg intravenously) was given just before the intravenous injection, at zero time, of tabun (0.8 mg/kg) (broken lines) or of sarin (0.22 mg/kg) (solid lines). Treatments, given intravenously at 5-minute intervals: (i) WIN 12306, 1 mg/kg; (ii) N-benzyl atropinium chloride, 5 mg/kg; (iii and iv) 2-PAM, 5 mg/kg.

is even faster and more complete within the duration of our experiments than that produced by N-benzyl atropinium chloride.

Administration of graded doses of anticholinesterase to groups of six rabbits, followed by treatment of the same rabbits by no other procedure than intravenous injection of either 5 mg of 2-PAM per kilogram, 2 mg of atropine sulfate per kilogram, a mixture of 2 mg of atropine sulfate and 5 mg of 2-PAM per kilogram, or nothing, has yielded approximations of the LD_{50} of sarin with various drug therapies. The LD_{50} of sarin for rabbits that are given no treatment is 16 μg/kg; for rabbits that are treated with 2-PAM alone, 24 μg/kg; for those treated with atropine alone, 51 μg/kg; and for those treated with both atropine and 2-PAM, 331 μg/kg. This last figure is based on results from 13 groups of rabbits poisoned with doses of sarin ranging from 64 μg/kg to 1.2 mg/kg.

Even with the highest dose of sarin, the combined treatment with atropine and 2-PAM saved one rabbit from the two groups of animals (12 rabbits) so poisoned and treated. None of the other treatments saved any animals at doses of sarin above 130 μg/kg, although combined treatment with atropine and 2-PAM saved 30 of 66 rabbits that were given doses of 160 or more μg/kg of sarin. Chemical treatment, to be effective after large doses of anticholinesterase, must be instituted within 1 minute after sarin injection.

It is apparent that 2-PAM alone, in the dose used, is a less effective therapeutic agent in anticholinesterase poisoning than atropine, but that it and atropine together make a very effective therapeutic combination. This conclusion supplements that reached by T. A. Loomis (*6*), namely, that 2-PAM is not significantly therapeutic in animals that are poisoned by sarin and given no other treatment.

If the effectiveness of 2-PAM as an adjunct to atropine in treating anticholinesterase poisoning is attributable primarily to its ability to overcome neuromuscular block elicited by the cholinesterase inhibitors, it is easy to see why 2-PAM is of little value alone. Death in animals that are not treated with atropine or other anticholinergic tertiary amines is caused, in large part, by central respiratory failure (*7*). Because 2-PAM is a quaternary amine, it would not be expected to pass the blood-brain barrier and to affect the activity of centers within the brain. Even though the 2-PAM were capable of overcoming all the other peripheral effects of anticholinesterase compounds, in addition to restoring neuromuscular transmission, it could not benefit the poisoned subjects in the face of continued central respiratory inhibition (*8*).

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11 February 1957

Echo Virus Type 9 (New Member of Coxsackie Group Type A?) as a Cause of Epidemic Meningitis

Last summer, an extensive epidemic of aseptic meningitis occurred in many parts of Western Europe: as far as we know, in Belgium, the Netherlands, Germany, Switzerland, England, and Denmark. This disease was characterized by meningeal symptoms (sometimes accompanied by exanthem), always with a very marked pleocytosis (up to 5000 cells/mm^3) and by its highly contagious nature; often all the members of a family, children and adults, were affected.

From 399 patients with the typical syndrome, 190 virus strains were isolated from fecal specimens, 29 from spinal fluids, and 6 from throat swabs. Proof of the etiologic significance of these virus strains was obtained by direct isolation from cerebrospinal fluid and by showing a rise of fourfold or more in the titer of neutralizing and complement-fixing antibodies in all paired serums of the patients examined (to date, 112 have been examined for neutralizing antibodies and 37 for complement-fixing antibodies).

No antibodies were found in serums from patients suffering from nonparalytic poliomyelitis (13 patients), paralytic poliomyelitis (19 patients) or atypical

pneumonia (9 patients), and none were found in 72 serums from healthy individuals. These virus strains were found to be cytopathogenic in primary tissue cultures of various cell types. They caused complete destruction of cultures of human amniotic cells and about 50 percent destruction of monkey kidney cells, and they had a moderate cytopathogenic effect in cultures of fibroblasts from monkey testis and epithelial cells from monkey epididymus. No effect was seen on the following cell types in continuous culture: HeLa, two strains of human kidney epithelium (adult and fetal), human lung fibroblasts, strain KB (Eagle) (*1*), conjunctiva (*2*), human intestine (*2*), and human liver (*2*), mouse mammary carcinoma cells (strain Ma Ca, de Bruyn), and normal mouse kidney epithelium.

The cytopathogenic effect of all these strains was prevented by neutralization with rabbit antiserum ECHO type 9 (*3*). Conversely, two standard ECHO type 9 virus strains (*4*) were neutralized by several rabbit serums against Belgian strains and by serums of human convalescents.

Most of these strains, as infected tissue culture fluid, produced myositis in suckling mice at least up to the age of 10 days: Many caused paralysis and some even death. Several of these strains, however, did not cause histologically detectable myositis. The two aforementioned standard strains belonged to the last group.

When a mixture of infectious tissue culture fluid and anti-ECHO type 9 serum was injected into suckling mice, no myositis occurred, while controls without immune serum died or were paralyzed. In the complement-fixation test, antigen prepared from aqueous suspension of baby mice was even better antigen than tissue culture fluid.

On histological examination of infected baby mice, no lesions other than those of myositis were found. The virus content of 10-percent suspensions of different tissues was determined in tissue culture; muscle contained about 10^6 TCD_{50}/ml, while brain, liver, kidney, and spleen contained from 10 to 10^2 TCD_{50}/ml. Up to now, three strains tested were not pathogenic for adult mice.

Ten original fecal specimens from which virus was isolated in tissue culture and found pathogenic for suckling mice did not cause any clinical symptom on direct inoculation into these animals; lesions were, however, detectable, histologically. A Belgian prototype strain was not neutralized by Dalldorf's antiserums against Coxsackie types A_1 to A_{17} and A_{19} and B_1 to B_5.

Considering these facts, we feel justified in proposing that the viruses of ECHO type 9 should be removed from the ECHO group and reclassified, probably as a new member of the Coxsackie A group of viruses.

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Notes

1. From H. Eagle.
2. Supplied by Microbiological Associates.
3. Kindly sent by A. Sabin.
4. Received through the courtesy of H. v. Magnus and A. Svedmyr.

31 January 1957

Induced Copulation of Aedine Mosquitoes

Aedine mosquitoes that develop in floodwaters are difficult to maintain as colonies in cages because conditions conducive to copulation are rarely attained. An efficient procedure for stimulating copulation has been devised in our laboratory, and by this means viable eggs have been obtained from *Aedes stimulans* and *Aedes vexans*.

Copulation is induced by manipulating an immobilized female into contact with a decapitated male. From the literature we learned that decapitation of males of mantids removed the center for inhibition of the copulatory act (*1*). Female mantids often eat the heads from their suitors prior to or during copulation, yet the act goes forward normally. Roeder (*2*) has shown that the center of inhibition in mantids is in the subesophageal ganglion. Removal of the head of male mosquitoes removes the ganglion also.

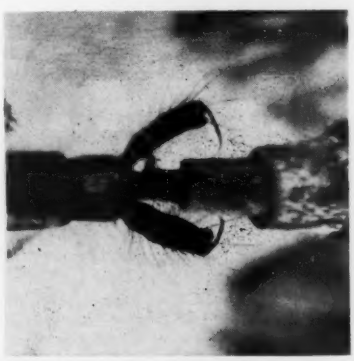

Fig. 1. Ventral view of male and female of *Aedes stimulans* in act of copulation (×18).

Mosquitoes that had emerged for a time greater than 72 hours were prepared for mating as follows. Females were anesthetized by exposure to atmospheres of either carbon dioxide or chloroform. The dorsum of the thorax of each was cemented to the tip of a fine needle. Several were prepared at each time and held until ready for use. Males were decapitated without prior anesthesia. Each of them was immobilized by cementing the dorsum of the thorax to a piece of white cardboard. Several of these could likewise be prepared at once before mating the series.

Contact between two immobilized mosquitoes was accomplished manually under a stereomicroscope magnifying about 20 diameters (Fig. 1). Each female was placed in mating position with its ventral side up and its head directed away from the male. Apexes of the two abdomens were then brought together. The position thus was end to end and venters uppermost. Insemination was usually completed within a few seconds.

The females were not injured by the treatment. The kind of cement used to attach them to the needles is not critical as long as it sets within a minute or two and can be loosened after copulation.

Techniques employed here permit matings at a rate of about 25 females an hour. This rate is reasonable for maintenance of even a large colony of one species or small colonies of several species. Since the eggs may be kept for months, they may be accumulated for large-scale experiments.

It was found that males would copulate with several females but that sperms were transferred dependably to only the first two. A large series of single matings resulted in insemination of 90 percent of the females. A comparable series in which males were mated a second time resulted in transfer of sperms to 85 percent of the females. When the males were mated a third time, only about half of the females were inseminated.

Attempts to inseminate *Culex pipiens* and *Anopheles quadrimaculatus* in this manner met with little success. A contributing factor seems to be differences in genitalia. Proper contact is difficult to establish, and the sperm mass rarely enters the genital opening of the female.

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25 February 1957

National Academy of Sciences

Abstracts of Papers To Be Presented at the Annual Meeting, 22–24 April 1957, Washington, D.C.

Thyroxin, Transhydrogenase, and Oxidation of Reduced Triphosphopyridine Nucleotide

Previous reports from our laboratory have dealt with a purified preparation from heart muscle which contains all the components of the cytochrome electron transmitter system. Electron micrographs of this preparation taken by Russell Barrnett indicate that it is composed largely of mitochondrial membranes. In the presence of this preparation, succinate and DPNH react rapidly with oxygen, but no reaction whatsoever occurs with TPNH, whether it is added as such or is generated by the glucose-6-phosphate dehydrogenase system. However, oxidation of TPNH does occur if a small amount of DPN is added. It thus appears that the preparation lacks TPN-cytochrome c reductase but contains the enzyme transhydrogenase, which catalyzes the reaction.

$$TPNH + DPN \rightleftharpoons DPNH + TPN$$

This DPN-mediated oxidation of TPNH requires cytochrome c and is inhibited by cyanide and the naphthoquinone SN 5949. The pathway of electron flow is thus characteristic of that for the oxidation of DPNH or succinate by the same enzyme preparation. A 30-percent and 85-percent inhibition of this oxidation of TPNH has been obtained with L-thyroxin at concentrations of $4.5 \times 10^{-6} M$ and $4.5 \times 10^{-4} M$, respectively.

Experiments are under way to see whether this inhibition by thyroxin occurs *in vivo*. If so, it could lead to an increase in the amount of TPNH oxidized by the alternate TPNH-cytochrome c reductase pathway and so induce a rise in activity of this reductase [see Philips and Langdon, *Biochim. et Biophys. Acta* **19**, 380 (1956)]. If this alternate pathway is less productive of high-energy phosphate [see Kaplan *et al.*, *Proc. Natl. Acad. Sci.* **42**, 481 (1956)], an increased oxygen consumption in the hyperthyroid animal would follow.

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On the Structure of an Intermediate in the Demethylation of Lanosterol

In the conversion of lanosterol to cholesterol by animal tissues, three methyl groups are oxidatively removed. The sequence of steps in this demethylation process has been partially elucidated by the isolation of a sterol of a hitherto unknown type. The new sterol is an efficient precursor of cholesterol. Although it is available only in trace amounts, the substance could be structurally characterized and shown to be a 4,4-dimethyl cholestadienol (14-nor-lanostadienol). Of the two double bonds in the molecule, one is located between C_{24} and C_{25}; the other, though not yet definitely assigned, is known to extend from C_8 to either C_7, C_9, or C_{14}.

Clarification of this remaining structural detail is being attempted by organic synthesis of the three isomeric 4,4-dimethylcholestenols under consideration. The natural sterol, labeled with C^{14} by biosynthesis and after conversion to the 24,25-dihydro derivative, cocrystallizes and is chromatographically identical with 4,4-dimethyl-$\Delta^{8,14}$-cholestenol. It is shown to differ, by the same procedures, from the $\Delta^{7,8}$ isomer. The mechanism of the demethylation of lanosterol is discussed in the light of these findings.

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Group Vibrations

Many complex molecules contain "characteristic groups," such as CH_3, whose group frequencies and approximate vibrational modes are reasonably well known in advance of calculation. A method is desirable whereby these "group vibrations" may be eliminated from the vibrational problem once and for all, in advance, and whereby the reduced problem of "framework" vibrations may be simply written without considering the complete molecular problem. This paper presents such a method and illustrates its application.

BRYCE CRAWFORD, JR., WILLIAM T. KING
University of Minnesota

Regulation of Gastric Secretion

Food taking stimulates gastric secretion by reflexes over the vagus nerves and through the liberation of a secretory stimulating hormone from the antrum of the stomach. When the acidity of the stomach contents reaches *p*H 3, further secretion is inhibited. This inhibition is due to the prevention of the formation and release of gastrin rather than to the release of an inhibitory hormone. When acidified food reaches the duodenum, pancreatic secretin is liberated. This hormone stimulates pancreatic secretion and, at the same time, inhibits gastric secretion dependent on the stimulating action of gastrin. There is thus a protective mechanism which under normal conditions prevents exposure of the stomach and duodenum to excessively acid gastric content.

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HERBERT B. GREENLEE,
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Dependence of Yield of Photosynthesis in Long-Wave Red on Wavelength and Intensity of Supplementary Light

The yield of photosynthesis of the green alga *Chlorella* from a band of red light centering at about 644 mμ is not increased by supplementing the red light with additional illumination from a different source. We have tried supplementary illumination at wavelengths from 644 mμ to 436 mμ and intensities sufficient to give photosynthesis approaching 10 times the rate of respiration.

On the other hand, the yield of photosynthesis from a band of red light of longer wavelengths (most of the energy being of wavelengths longer than 690 mμ) can be increased by supplementary light of shorter wavelengths. We have measured the increase in yield as a function of intensity and wavelength of the beam of supplementary light. Higher intensities of supplementary light lead to greater improvements in yield of photosynthesis from long-wave red up to a point of saturation.

To compare different wavelengths of supplementary light, we used intensities below the region of saturation. At each wavelength we adjusted the intensity of the supplementary beam to give the same rate of photosynthesis. We then measured the increment in photosynthesis brought about by addition of the band of long-wave red light. Of wavelengths so far tested, the yellow mercury line at 578 mμ is most effective, the red cadmium line at 644 mμ is next, followed by the green mercury line at 546 mμ. Least effective is the blue mercury line at 436 mμ.

Comparison of these observations with the absorption spectra of chlorophylls *a* and *b* shows that there is a possibility of interpreting the differences in effectiveness of different wavelengths as evidence that chlorophyll *b* is the sensitizer for the action of supplementary light.

The collaboration of Ruth Chalmers and Carl Cederstrand and support from National Science Foundation grant G-1398 are gratefully acknowledged.

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Color Discrimination by the Turtle Retina

The retinas of fresh-water turtles have few rods, and their function is dominantly that of cones. Earlier experiments showed

that a sudden shift of illumination from one color to another evokes an electric response that cannot be abolished by any balancing of intensities [Forbes *et al., J. Neurophysiol.* **18**, 517 (1955)]. We have conducted two kinds of experiments to determine what types of receptors are involved.

Spectral sensitivity curves were calculated from the height of electroretinograms recorded with gross electrodes from the excised, dark-adapted retina. With moderately bright light, peak sensitivity occurred at about 645 mμ, with shoulders at approximately 620 mμ and 575 mμ. With extremely dim light, peak sensitivity lay somewhere in the blue-green.

Quantitative study of the shift response in relation to difference in wavelength between two beams was made with one of four interference filters for the fixed color (675, 570, 540, and 510 mμ) and a monochromator for the variable color. The energy of the two sources was adjusted to equalize the height of the on-effect *b*-waves. Shifts from the fixed to the variable color and back produced larger responses as the difference in wavelength became greater. Increases in size of shift response occurred in steps. These rises were steepest at 620 to 640 mμ, 585 to 605 mμ, and 540 to 560 mμ, suggesting the activation of three types of cones, sensitive to red, orange, and yellow-green, and rods, sensitive to blue-green.

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Element Synthesis in Supernovae

On the assumption that an intense flux of neutrons ($\sim 10^{32}$/cm^2 sec) becomes available in a supernova explosion [F. Hoyle *et al., Science* **124**, 611 (1956)] heavy elements ($A > 60$) are synthesized, primarily from the iron group elements, by a rapid succession of neutron captures interspersed with negative beta decay. The capture path in the charge-mass (Z–A) plane passes through unstable neutron-rich nuclei whose neutron binding energies (~ 2 Mev) are such that equilibrium is reached between the (n,γ) and (γ,n) processes involving these nuclei at the temperature ($\sim 10^9$ degrees) and neutron density ($\sim 10^{24}$/cm^3) at which synthesis takes place. Abundances have been assumed to be proportional to the beta decay lifetimes ($\tau_\beta \sim W_\beta^{-5}$), which have been calculated for these nuclei by using extrapolations of empirical beta decay energies (W_β).

Reasonable agreement is found with the abundances of Suess and Urey [H. E. Suess and H. C. Urey, *Revs. Modern Phys.* **28**, 53 (1956)] for the neutron-rich stable isobars at a given A which result from the subsequent beta decay of the nuclei produced at A. The abundance peaks at $A \approx 80$, 130, and 196 have been attributed [C. D. Coryell, *Lab. for Nuclear Sci. Ann. Rept.* (1956); P. Fongg, *Bull. Am. Phys. Soc.* **2**, 15 (1957)] to neutron magic numbers $N = 50$, 82, and 126. The critical dependence of the shape of these peaks on the conditions at synthesis raises the question whether the observed neutron-rich heavy nuclei of the solar system might have been produced in a single supernova.

Supernova synthesis is capable of building radioactive elements, and we have calculated the relative abundance of the progenitors which decay to U^{235} and U^{238} by subsequent beta and alpha decay. The production ratio is $U^{235}/U^{238} = 1.8$, assuming that spontaneous fission occurs rather than alpha decay for A (odd) $\geqq 259$, A (even) $\geqq 250$. From the present U^{235}/U^{238} ratio and the relative decay rates, it is thus possible to calculate the date of a single-event synthesis as 6.7×10^9 years ago. Synthesis in a series of supernovae requires an even longer time scale, $\sim 10^{10}$ years.

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California Institute of Technology

Genetic Control of Adenylosuccinase in Neurospora crassa

Combined genetical and biochemical studies have been performed on a series of adenine-specific mutants in *Neurospora crassa*. Twenty-one mutants of independent origin have arisen as a result of mutation at a single locus (*ad-4*) in linkage group III between two closely linked marker genes. Crosses between the various mutants tend to be sterile and yield few or no homocaryotic adenine-independent recombinants. Biochemically, all the mutants have been found to be blocked in the terminal step in adenine biosynthesis, involving the splitting of adenosine monophosphate succinate (AMP-S) to adenosine monophosphate (AMP) and to lack or have impaired activity for the AMP-S splitting enzyme, adenylosuccinase. One of the mutants is temperature sensitive and produces an adenylosuccinase which in crude extracts is much more thermolabile than that from wild type. Certain of the *ad-4* mutants are capable of reverse mutation to adenine-independent phenotypes, and these have been shown to possess restored adenylosuccinase activity, although at levels (or of stabilities) below that of wild type.

These results establish that in this instance forward mutation at a single locus in the wild type to adenine requirement results in the loss of activity of a specific enzyme involved in adenine biosynthesis, and that reverse mutation to adenine-independence results in the restoration of this activity. Additionally, changes at this locus, arising from either forward or reverse mutational events, may produce diverse mutant and revertant types as judged by qualitative and quantitative tests of enzyme activity.

Certain combinations of *ad-4* mutants have been found to form heterocaryons (dicaryons) able to grow in the absence of adenine. Although the individual mutants lack detectable adenylosuccinase activity, this enzyme is synthesized by the dicaryons. Possible mechanisms for this unexpected type of complementation between alleles in enzyme formation are considered along with its implications for biochemical genetic theory in general.

NORMAN H. GILES, C. W. H. PARTRIDGE,
NORMA J. NELSON
Yale University

Experimental Investigation of the Effect of Air Pollution on the Initiation of Rain

Warm or unnucleated supercooled clouds will not usually precipitate unless moderate numbers of large cloud droplets (about 15 to 25 μ radius) are formed high above the cloud base. These droplets fall down through the cloud and grow into raindrops by accretion.

New measurements in a giant expansion chamber show that the size of newly formed cloud droplets depends critically on the cleanliness of the processed air. Droplets formed in ordinary air are too small to grow, but droplets large enough to precipitate are immediately formed by condensation whenever the condensation nuclei density is sufficiently reduced. Since the activated nuclei density is usually observed to decrease rapidly with increasing altitude, the probability of generating droplets sufficiently large to initiate rain increases as the vertical development of a cloud system increases. The population densities of the large cloud droplets usually observed near the tops of precipitating clouds may be explained in terms of the cooling of an overlaying parcel of air that is initially relatively free of nuclei.

Since pollution is swept out of the atmosphere by diffusion onto cloud droplets and by droplet movement, it is suggested that periods of general cloudiness and precipitation act to reduce the original nuclei density. This permits the subsequently formed droplets to grow still larger, thus increasing the probability of appreciable precipitation. The rain-producing cycle is, therefore, provided with a feedback or regenerative mechanism which usually proceeds, in a given mass of air, until the air is appreciably desiccated.

Condensation nuclei, as well as water vapor, usually accumulate simultaneously in fair weather. The presence of these nuclei may delay the initiation of precipitation until sufficient vertical instability can be established to lift or cool the relatively clean overlaying layers. The precipitation cycle may then be reestablished.

ROSS GUNN, B. B. PHILLIPS
U.S. Weather Bureau

Effects of Ground on Shaking in Earthquakes

Damage from earthquakes depends on properties of earthquake waves, effects of the ground (investigated here), and properties of the shaken structures. Five identical seismographs have been operated temporarily at about 20 locations near Pasadena, and their records have been compared with those of an identical rou-

tine instrument at the Pasadena Seismological Laboratory of the California Institute of Technology.

The ratio of amplitudes recorded at locations on fairly dry alluvium more than 500 feet deep to those written simultaneously at the Seismological Laboratory (on crystalline rock) is frequently 5 or more for earthquake waves having periods of about 1 sec. For much shorter waves (periods of ± 0.1 sec) and much longer waves (periods of more than 10 sec, length more than 10 mi) the corresponding differences in amplitudes are usually small. On water-saturated soft ground amplitudes may be more than 10 times those recorded at the laboratory. Usually the period of waves for which the relative response is greatest decreases as the thickness of the alluvium decreases and is about ¼ sec at stations on alluvium ± 100 feet thick. On Mount Wilson (on crystalline rock) the ground motion is slightly greater than at the laboratory.

On alluvium relatively strong shaking lasts a few times as long as on crystalline rock; usually, its duration in a given shock decreases with decreasing thickness of the alluvium. Ground effects may produce appreciable differences in duration and amount of shaking at sites less than 1 mi apart.

B. GUTENBERG
California Institute of Technology

Cross-Reactions of Anthrax and Cryptococcus-A Polysaccharides in Type-XIV Antipneumococcal Horse Serum

Anthrax polysaccharide from bacilli grown in guinea pigs precipitated the antiserum, while that from *in vitro* cultures did not. Forssman antigen, known to cross-react, was not responsible, since absorption of the antiserum with sheep erythrocytes did not prevent the precipitation. Removal of antibody precipitated by anthrax greatly reduced precipitation by carob mucilage, a galactomannan in which galactose occurs only as nonreducing end-groups. Carob-absorbed antiserum also gave less precipitate with anthrax. Galactose end-groups might, therefore, account in part for the cross-precipitation, particularly since the type-XIV pneumococcal polysaccharide, the antigenic determinant responsible for the production of the antibodies under investigation, has now been found to contain the galactose end-groups predicted from the cross-reactions of carob and tamarind seed polysaccharides in type-XIV antipneumococcal serum. It is therefore likely that the anthrax polysaccharide also contains galactose end-groups.

The specific polysaccharide of cryptococcus A was found by Evans to contain mannose, xylose, glucuronic acid, and a little galactose, present possibly as a contaminant. The cross-reaction of the polysaccharide in anti-XIV was used in order to resolve this question. Comparison of the original and antibody-precipitated substances showed that the latter (2 percent) contained 3 times as much galactose, twice the glucuronic acid, and one-half as much mannose as the original material. This therefore contains at least two polysaccharides, one richer in galactose and glucuronic acid than the other. Quantitative data on these findings are given.

M. HEIDELBERGER
Rutgers University
S. A. BARKER
University of Birmingham, England
P. A. REBERS
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Inhibition of Growth of Mammary Tumors of the Rat by Administration of 3-Methylcholanthrene

In the present experiments on neoplasms of the albino rat, it was found that 3-methylcholanthrene retards the growth rate of transplanted mammary tumors owing, in part, to a selective depression of certain functions of the hypophysis.

Certain mammary tumors are characterized by a high degree of dependence on ovarian hormones, since their growth is profoundly retarded by ovariectomy or by the administration of certain compounds in the androstane series. The administration, oral or intramuscular, of 3-methylcholanthrene, 2 mg daily for 50 days, caused a considerable depression of growth of these tumors.

Other mammary tumors are more malignant than the afore-mentioned ones, since their growth rate is more rapid and it is little affected by the removal of the ovaries. The administration of androstane derivatives or 3-methylcholanthrene restrained the growth of these tumors only slightly. The concurrent injection, daily, of dihydrotestosterone (1 mg) and 3-methylcholanthrene (2 mg) caused a profound depression of the growth of these malignant tumors.

With reference to uninjected controls the administration of 3-methylcholanthrene, 2 mg daily for 50 days, resulted in a decrease of weight of ovaries, uterus, preputial glands, and the hypophysis. Estrus was not always abolished. Body growth was not significantly retarded, and the adrenals were similar to the controls. 3-Methylcholanthrene caused a profound decrease of content of alkaline phosphatase in the mammary glands of the tumor hosts. The compound did not promote growth of hormonal targets.

CHARLES HUGGINS, LUCIO POLLICE
Ben May Laboratory for Cancer Research, University of Chicago

Action of Thyroxin on Mitochondria

It has been postulated that the primary action of the thyroid hormone is to act as a biological uncoupling agent since thyroxin added *in vitro* under certain conditions inhibits the phosphorylation of ADP which is coupled to respiration in isolated mitochondria. However, reports from this laboratory have established that thyroxin does not have a detectable inhibitory action on the enzymes involved in coupled oxidative phosphorylation as it occurs in fragments of the mitochondrial membrane separated from digitonin extracts of mitochondria. On the other hand, it has been shown that thyroxin does cause changes in the structure of isolated mitochondria, leading to uptake of water and swelling.

This paper deals with a more detailed study of the action of thyroxin on the structure of rat liver mitochondria *in vitro*. With some refinement of experimental conditions, the swelling action of thyroxin can be detected at a concentration of $1 \times 10^{-8} M$, which is approximately that existing in the tissues. A number of factors influence this reaction, among which are *p*H, ionic, and non-ionic constituents of the medium and tonicity. The reversibility of the action of thyroxin is considered. The oxidation-reduction state of the respiratory carrier enzymes of the mitochondria appears to be a major factor in conditioning the response of the mitochondria to thyroxin and also the rate of the exchange of inorganic P^{32} with ATP. These findings suggest that the action of thyroxin on mitochondria is on factors linking the enzymes concerned in electron transport and phosphorylation with what appear to be contractile elements of the mitochondrial membrane.

ALBERT L. LEHNINGER, BETTY LOU RAY
Johns Hopkins School of Medicine

Learning Elicited by Electric Stimulation of Subcortical Regions in the Unanesthetized Monkey

It has been demonstrated that an animal can learn to operate a switch in order (i) *to start* a train of electric stimuli [Olds and Milner, Brady *et al.*] or (ii) *to stop* a train of stimuli [Delgado, Roberts and Miller] in different regions of the unanesthetized brain. In our experiments, we have tested and mapped approximately 500 zones in the brains of three restrained, unanesthetized monkeys (*Macaca mulatta*) within approximately 6 mm of the midplane in experiments lasting from 3 to 12 months. The "start-the-stimulus" zones are found to be much more numerous than the "stop-the-stimulus" ones.

To date, "start" zones can be found in the septum, caudate, globus pallidus, and putamen; "stop" zones, in the preoptic and anterior hypothalamic regions. To date, most of the neocortex appears to be relatively neutral.

Stimulation of a "start" zone can function as a reward for lever pressing, alternation, delayed alternation, and quasi-counting. With a proper choice of stimulus parameters, stimulation of a "stop" zone can be shown to function as a punishment; the animal can learn to turn off the stimulus train without any external clues and without exhibiting any of the clinical signs of "fear" or "pain" which are elicitable at higher values of current. In most of the "start" zones, mild "searching" or "hallucinating" behavior is elicited and attack or escape actions are inhibited. In the "stop" zones, either pain-

like or fearlike behavior can be reproduced in different regions with inhibition of feeding, grooming and similar types of spontaneous activity. During stimulation of these animals, the various clinical syndromes elicited do not allow a secure diagnosis of either the presence or absence of a subjective concomitant.

JOHN C. LILLY
National Institute of Mental Health

Behavior of Two Protein Antigens in Mice during Inhibition of Antibody Formation by Cortisone

This report describes an attempt to learn more about the mechanisms of antibody formation by determining whether or not certain procedures that inhibit the process achieve this end by affecting the way in which the body deals with antigens.

The dosage of cortisone large enough to inhibit all antibody formation in mice, which were vigorously stimulated to form antibody, was first determined. Other mice, while under the influence of this dosage of the hormone, were then injected with a tracer antigen obtained by coupling a blue dye to bovine γ-globulin. In these animals, the spleens and lymph nodes, organs which normally form antibody, were reduced to about one-sixth or one-eighth of their usual weight, and no antibody was formed. Nevertheless, these diminutive organs, and other tissues throughout the body which were relatively unaffected by cortisone, took up quite as much of the tracer antigen as was found in the same tissues of normal animals. Moreover, mice injected with the native protein, bovine γ-globulin, instead of the tracer antigen, while under the influence of cortisone—and maintained under its influence and unable to form antibody for 3 weeks—readily produced antibody when the hormone was withdrawn.

Apparently, the cortisone did not inhibit antibody formation by affecting the ability of the tissues to take up the tracer antigen, nor was the antigenicity of the native protein, bovine γ-globulin, destroyed more rapidly than it seems to be in normal animals.

PHILIP D. MCMASTER
Rockefeller Institute for Medical Research
JOSHUA L. EDWARDS
University of Florida College of Medicine

Interaction between Tobacco Mosaic Virus and Formaldehyde

The rate of reaction of formaldehyde with a masked strain of tobacco mosaic virus (1 mg/ml) was determined at three temperatures by means of HCHO—C^{14} in nine concentrations ranging between 25 μg HCHO/ml and 19.86 mg/ml. At all concentrations, relatively rapid initial reaction was followed in approximately 15 hours by a slower increase in formaldehyde uptake which was observed to be linear in time. After 3 to 4 days the reaction became still slower but never ceased during the 36 days' duration of these experiments.

The slopes (F) of the intermediate linear portion of the reaction curves, as well as the intercepts (I) with the ordinate, were proportional to initial formaldehyde concentration (C_0). This behavior suggests the intervention of a diffusion process. Considering the virus as an infinite cylinder, application of diffusion mathematics to the case of simultaneous radial diffusion (diffusion coefficient D cm^2 sec^{-1}) and irreversible first-order reaction with respect to formaldehyde (k sec^{-1}) within the virus leads, after simplification, to the following expression for formaldehyde retention (M_t) in micrograms per milliliter of virus at time t:

$$\frac{M_t}{C_0} = 0.278\left[1 + kt - \left\{\sum_o \frac{-Da_n^2 t}{a_n^2}\right\}\frac{1}{\sum\frac{1}{a_n^2}}\right]$$

from which values of k and D may be deduced. Here a_n's are obtained from roots of the Bessel function $J_0(ra_n) = 0$ in which r theoretically is the radius of the cylindrical virus. Experimental values of $\Sigma 1/a_n^2$ correspond to a diffusion path shorter than the actual radius. The activation energy of the reaction is 9000 to 10,000 cal/mol. The maximum formaldehyde retention observed was 8.4 μg/mg after 36 days at $C_0 = 9950$ μg/ml, which corresponds to 14,000 molecules of HCHO per TMV molecule (mol wt. 5×10^7).

HENRY T. MERIWETHER,
CHARLES ROSENBLUM
Merck, Sharp & Dohme
Research Laboratories

Experimental Study of Increased Susceptibility to Salmonella Infection following Antibiotic Therapy

Mice which have been treated the day before inoculation with a single large dose of streptomycin by stomach tube can be infected (by stomach tube) with about one 100-thousandth of the number of *Salmonella enteriditis* required to infect normal untreated mice. This increased susceptibility to *Salmonella* infection is believed to be caused by some change in the composition of the normal microflora of the intestinal tract resulting from the antimicrobial action of the drug. It is presumed that the normal intestinal flora includes microorganisms which in some way hinder the establishment of *Salmonella*.

In vitro, the multiplication of *Salmonella* is inhibited by bacteria-free filtrates of suspensions of feces from normal mice but not by similar filtrates of feces from streptomycin-treated mice. This inhibitory effect is demonstrable only under anaerobic conditions. It does not occur under aerobic conditions, or in the presence of an abundant supply of nutrients. The enhanced susceptibility of streptomycin-treated mice can be reduced by introducing into the gastrointestinal tract fecal suspensions from normal mice or anaerobic cultures of such suspensions.

Our observations thus far suggest that the presence of certain Gram-negative, nonsporulating, streptomycin-sensitive anaerobes in the mouse's intestinal tract acts as a deterrent to the establishment of *Salmonella*. If this be true, their presence must play a significant role in the maintenance of the normal degree of resistance to infection with this microorganism which is a natural pathogen for the mouse.

C. PHILLIP MILLER,
MARJORIE BOHNHOFF, DAVID RIFKIND
University of Chicago

Some Differences in the Stellar Population of Galaxies

Recent work carried out jointly with N. U. Mayall at the Mount Wilson and Lick Observatories indicates that there is a well-marked relationship between the spectra and forms of the galaxies. Those having pronounced nuclear bulges seem to owe most of their light to yellow giant stars; on the other hand, systems with little or no central condensation are composed principally of blue and white stars —as far as their light is concerned.

These differences in stellar types are probably associated with different stages in evolutionary development. A promising field for investigating the physical nature of galaxies is indicated from studies of galactic spectra.

W. W. MORGAN
Yerkes Observatory

Ocean Waves of Very Low Frequency

We have obtained some energy spectra of pressure fluctuations on the sea bottom at a depth of 60 fathoms off Guadalupe Island, Mexico. For frequencies higher than 1 cycle in 20 seconds, the spectra consist of peaks whose frequency increases by about 10 percent per day; sequences repeat once every 3 or 4 days. These dispersive signals are believed to originate from very distant cyclones in the storm belt of the Southern Hemisphere. The earliest arrivals are of the order of 1 mm high and 1 km long; there is some indication that they originated in the Indian Ocean and have traveled through the Tasman Sea. Later arrivals were generated in the South Pacific. For frequencies lower than 1 cycle in 20 seconds, the spectra reveals a series of well-defined bands with fine structure. The features repeat themselves from day to day without changes in any essential details.

WALTER H. MUNK, FRANK SNODGRASS
Scripps Institution of Oceanography

Heteroplastic Grafting between Rat and Chick Embryos

Martinovitch has shown that experiments utilizing auto- and homografts can be performed in chick embryos before the establishment of the circulatory system. In the light of this work, it was deemed necessary to reinvestigate heteroplastic

grafting between widely different species to test the capacity of tissue healing, to test the capacity for graft differentiation, and to test the current theories of tissue specificity.

Rat embryos of varying ages were transplanted into chick embryos after the host had been prepared for the transplantation by the excision of the forebrain at the mid-mesencephalic level. The tissues of the host and graft heal well initially and, in the best cases, form masses which are chimerically combined with the tissues of the host. When it is only partially connected with the host, the graft may form an independent embryonic vesicle.

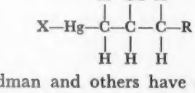
Differentiation occurs in the graft tissues definite with reference to both specific tissues and organs. It is more nearly complete than in chorioallantoic grafts, and specific embryonic form is more frequently secured.

According to theories now current, the blood content is specific for graft tolerance. In our series, the fate of the graft is influenced by a number of factors of which vascularity is but one. There is not in the embryo the antagonistic specificity that has been reported for heterografts in adults.

J. S. Nicholas, Petar Martinovitch
Yale University

Structure-Diuretic Activity Relationships of Organic Compounds of Mercury

Mercurial diuretics in common use today exhibit certain basic similarities in structure. All are addition products of mercury and substituted propyl compounds and may be represented as follows:



Friedman and others have shown that the nature of OY within limits of hydroxy, methoxy, or ethoxy has little effect on the basic diuretic properties of these compounds. X, although a determinant of acute toxicity (cardiac arrhythmias), is otherwise of little significance. It is commonly halogen, theophylline, or thioglycollate. R, on the other hand, has a pronounced effect on both toxicity and diuretic potency. It is commonly a complex substituent, the simplest representative being urea in the compound Chlormerodrin.

Not all organic compounds of mercury have diuretic properties. In an attempt to define the simplest structure consonant with diuretic activity and to describe the essential pharmacological properties of such a drug, we have synthesized 12 organic compounds in which the mercury is attached by one valence bond to a 1, 2, or 3 carbon chain or to a benzene ring.

If one disregards mercuric chloride, which is moderately effective as a diuretic, the structure which we have found to be associated with diuretic activity includes (i) a chain of not less than 3 carbon atoms, (ii) an atom of mercury attached to the terminal carbon of this chain, and (iii) some hydrophilic group not less than 3 carbons distant from the mercury. It is possible that mercury and the hydrophilic group with this critical spatial configuration bind at two sites to some renal tubular enzyme concerned with reabsorption of salt and water. Inactivation of this enzyme results in diuresis.

Robert F. Pitts, Richard H. Kessler, Rodolfo Lozano
Cornell University Medical College

Scientific Apparatus: Unwritten Documents of the History of Science

Written and published accounts of experimental work tell only part of the story of scientific investigation. They reflect what the scientist thought he was doing; this, in some cases, may be very different from what was actually the case. At the time of making an experiment, one may be very conscious of the capabilities and limitations of one's apparatus, but later generations see the story divorced from this governing influence. Only by the study of former instruments can we fully relive the atmosphere of previous scientific work and gain an understanding of why and how things happened when they did. Too often, important pieces of apparatus have been lost by neglect and cannibalization; even in some cases where they have been preserved and cared for, they cannot be studied to advantage without a range of comparative material.

The role of the museum of science is thus more than a pedagogic device for teaching science or a reliquary of scientific heroes; it is an essential tool in our understanding of the way in which advances are made.

Examples are adduced from Classical Greece, from the Middle Ages, and from Modern Times to show how such evidence is important to studies of the history of science and even to science itself.

Derek J. Price
Smithsonian Institution

Normal Proclivities and Neoplastic Disabilities as Determinants of the Course of Tumors

Tumors are habitually appraised in terms of powers gained, not of lost powers or retained normal traits; yet their influence can bulk large.

Carcinogens elicit many "benign" epidermal excrescences on rabbit or mouse skin for every cancer arising. These papillomas are telltales of cancers to come, which take off from some of them; but they have failed heretofore on transfer and eventually regress unless stimulated.

Six papillomas from tarred mice, implanted subcutaneously in sucklings, have now flourished for more than a year in successive hosts, inducing no obvious resistance, and usually proving fatal. Single in kind, they differ in capabilities. Type-A tumors have able-bodied cells, keratinizing and spreading on bare surfaces, like normal epidermis. They line graft pockets with a velvety layer and pack them with keratin, thus turning the papillomas outside in. Keratin accumulation renders the cysts huge; the overlying skin mummifies; and the uninvasive growths, lacking anchorage, are extruded to the surface, forming massive horns there, broad, keratinizing discs, or giant papillomas.

Type-C tumors have crippled cells, unable to spread but producing keratin. This inflames the adjacent tissue, and an ever-enlarging, fluid-filled cyst forms, having bare walls except where a stalked or cauliflower papilloma protrudes. Eventually the cyst ruptures; fluid escapes; and fatal infection follows. Type C grades into type A. The many carcinomas derivative from both lack spreading power. Hence, those on the walls of type-A cysts are outstripped laterally by the extending papilloma tissue, which kills through incessant keratin production.

Peyton Rous, Raymond A. Allen
Rockefeller Institute for Medical Research

Ramifications of Studies on African Amphibians

Studies on the amphibians and reptiles of Africa, begun by one of us (K. P. S.) in 1916, continue in a formal report on a collection of some 70,000 frogs, of 40 species, from the Belgian Congo. The report is undertaken at the instance of Victor Van Straelen, director of the Institut des Parcs Nationaux du Congo Belge, and concerns material obtained in the new Parc National de l'Upemba, in the southeastern Congo.

New studies, with large series of specimens, make possible great improvements in the definition of the species, for secondary sex characters are defined, are followed through their ontogenetic and seasonal development, and are distinguished as genetic and hormonal. These studies have involved separate anatomical studies by one of us (R. F. I.).

The food habits of African frogs are for the first time examined with sufficient material to place chance records in perspective and to discern the seasonal cycle in foods taken.

The sharpened definition of the species of frogs brings us in contact with a remarkable "species swarm" in the subgenus *Ptychadena* of the common frog genus *Rana*. There are some 35 species of this group in Africa, of which a great number are sympatric. Their definition renews interest in the field ecology of many abundant forms.

Exact definition of the species involved brings out the geographic relations of the southeastern Congo. There is an east-west savanna province south of the central African forest, extending from Angola to Lake Tanganyika, corresponding to the east-west Sudanese province 1000 miles to the north.

Karl P. Schmidt, Robert F. Inger
Chicago Natural History Museum

On the Theory of the Bubble Chamber

The bubble chamber invented by Glaser employs superheated liquids in which bubbles are nucleated by the passage of charged particles. The mechanism of nucleation appears to depend on the production of point thermal "spikes" produced as a consequence of the transfer of kinetic energy from the moving particle to the electrons or nuclei of the liquid. Glaser [D. A. Glaser and D. C. Rahm, *Phys. Rev.* **97**, 474 (1955); D. A. Glaser, D. C. Rahm, C. Dodd, *ibid.* **102**, 1653 (1956)] and his colleagues have quoted an example in which about 16 bubbles were formed per centimeter of path in propane by positive pions having momenta near 900 Mev/c. This corresponds to a cross section per molecule in the range associated with the transfer of about 1 Kev or more to the electronic system by coulomb encounters, whereas it corresponds to the transfer of 0.1 ev or more to the protons.

Three components of energy enter into the formation of a bubble which can expand: (i) surface energy of the bubble, (ii) heat of sublimation of the gas in the bubble, (iii) energy required to sustain the pressure needed for production of the bubble in competition with thermal conductivity. In hydrocarbons and heavier rare gases, each of these appears to be of the order of 1 Kev under conditions described by Glaser and his associates. In hydrogen, the first two are of the order of 1 ev, whereas the third is nearer 100 ev and apparently is the limiting factor.

It is proposed that energetic electrons are responsible for the great majority of bubbles. Their kinetic energy is transferred to the molecules and produces localized thermal spikes in a sphere of radius 10^{-6} cm or less.

FREDERICK SEITZ
University of Illinois

High-Melting Fibers

Since early in 1951, I have been directing researches on the production of high-melting glass fibers. High-melting oxides and minerals and their mixtures have been changed to glass directly, since no classical glass-melting furnaces were capable of attaining the necessary temperatures. The raw materials were mixed with suitable binders, wetted and converted to a plastic mass that was extruded downward, in continuous rods or tubes, by a screw feed. These, on descending, were dried and baked by convection currents and then passed through suitably designed high-temperature burners. The lower end of the baked extruded material was melted instantly and homogeneously to glass, which was either blown by compressed air or steam into bulk fibers, or drawn into monofilaments.

A pilot plant has already produced 200 pounds per day of superior bulk fiber, which has remained unchanged after baking 2.5 days at 2350°F and subsequent storing for 3 years. These fibers are longer, softer and more durable than any others of approximately their nature resulting from earlier efforts in the fiber glass field. The capacity of the production unit can be increased to 1 ton per day.

Researches are underway toward the production of fibers with melting points up to and beyond 5000°F. Special heating systems, besides oxygen-acetylene, are under consideration.

The entire principle depends on the very rapid passing of transition points and the retention of high-temperature properties. The products are intended largely for use in jet craft and guided missiles.

ALEXANDER SILVERMAN
University of Pittsburgh

Magneto-Ionic Expander Isotope Separator Applied to Uranium

In the ionic centrifuge [J. Slepian, *J. Appl. Phys.* **26**, 1283 (1955)] and the magneto-ionic expander isotope separator [J. Slepian, *J. Franklin Inst.* (Feb. 1957)] the random energies of the ions and of the electrons remain equal to each other at each point of space; hence, these devices have no space-charge current limitation whatsoever. In the ionic centrifuge, however, the random energy of the ions goes up with the energy of mean motion of the ions. Hence, there can be only small enrichment of isotopes in the various deposits.

In the mageto-ionic expander, on the contrary, the large adiabatic expansion received by the ions and electrons makes their final random energy small compared with the energy of final mean motion of the ions. Hence, very high isotopic enrichment is found among the deposits.

When applied to uranium the cost per gram of U^{235} in the expander is approximately $\$1 + \$700/I$, where I is the number of amperes in the arc. We have used $I = 100$ experimentally, which would make the cost \$8 per gram of U^{235}.

At present the price per gram of U^{235} 90-percent enriched is \$17.07 as offered by the 1956 AEC price list. This is obtained by the multistage gaseous-diffusion process, to which the magneto-ionic expander is therefore a strong competitor.

JOSEPH SLEPIAN
Pittsburgh, Pennsylvania

Effect of Pressure on Electric Properties of Polymer Solutions

An apparatus for measuring the dielectric properties of liquids at pressures up to 1200 atm over the frequency range from 10^2 to 10^6 cy/sec has been constructed. The electric measuring system imitates that described by Cole and Gross. Our principal objective is to study relaxation processes in high-polymer solutions.

The effect of pressure on the dielectric constant and loss of a 50 weight-percent solution of poly-p-chlorostyrene in toluene has been determined over the temperature range from −20° to 30°C. The breadth of the dispersion region is slightly greater than that predicted by Kirkwood and Hammerle for a dilute polymer solution and is nearly independent of temperature and pressure in the range studied. At constant pressure, the temperature-dependence of the frequency of maximum loss corresponds to a heat of activation of 14 kcal/mole for the relaxation process, while the pressure-dependence at constant temperature gives a "volume of activation" of about 50 ml/mole.

With the aid of available density and compressibility data, we find that the aforementioned results correspond to an energy of activation of about 10 kcal/mole for the relaxation process at constant volume. This figure is much higher than constant-volume activation energies for diffusion, viscosity, or dielectric relaxation in simple liquids and suggests that energy barriers to internal rotation of the polymer chain play a significant role in limiting the relaxation rate.

WALTER H. STOCKMAYER,
MARTIN E. FULLER II,
ROBERT L. CLELAND,
JAY H. VREELAND
Massachusetts Institute of Technology

Energy Transmission in Biological Systems

Newer knowledge of the structure of contractile proteins makes it increasingly difficult to picture contraction as a classical chemical reaction. The possibility was considered earlier that the bond energy of ATP is transformed into electronic excitation ere it produces contraction. It was found that the steric relations of the ATP molecule are such as to make it possible for the terminal phosphate to form a coordination complex with the purine of the same molecule, the two being coordinated by a magnesium atom through which excited electrons could pass. The question of how the excitation energy is transmitted from purine to the contractile protein was left open.

Acridin orange can be excited by light to a singlet which emits a green fluorescent light. If two acridin orange molecules dimerize, then they are excited to a triplet which emits a red phosphorescence. If a glycerinated muscle is stained with acridin orange, as shown by Karreman and Mueller, it becomes red phosphorescent, indicating that the dye has formed a dimer with some constituent of the muscle proteins. The question arises whether ATP does not transmit its energy to the muscle proteins by dimerizing, similarly, with some group on the protein, the dimer thus formed being capable of a triplet excitation. If the hypothetical dimerizing group would be identical with the one binding acridin orange, then acridin orange should inhibit contraction and the inhibition should show the properties of competitive adsorption. The experiments show this actually to be the case.

These observations bring the possibility closer that ATP transmits its energy to

the contractile proteins by dimerizing with some group, possibly histidine, the dimer being capable of a triplet excitation into which the energy of the ~ P is transformed.

ALBERT SZENT-GYÖRGI
Marine Biological Laboratory, Woods Hole

Recrystallization Textures in Experimentally Deformed Marble

At 300° to 600°C and confining pressures of 3000 to 5000 atm, pure calcite marble is highly ductile. Shortening of cylinders by 50 percent and local elongation by 500 percent are achieved in experiments of 1 or 2 hours' duration. The main mechanism of deformation is plastic —twin gliding on $\{01\bar{1}2\}$ and translation on $\{10\bar{1}1\}$. This is accompanied by rotation of grains and adjustment of grain boundaries. The process and resultant microscopic fabric are closely analogous to those of cold-worked metallic aggregates. As in the latter, the component grains show strong preferred orientation, which attains a stable pattern in highly strained material.

Even at high temperatures (500° to 800°C) recrystallization involving growth from new nuclei is surprisingly inconspicuous, except in highly strained specimens. In these we have observed partial recrystallization within some grains; and in one specimen clusters of new granules have developed along old grain boundaries. Part, at least, of recrystallization occurred while deformation was in progress (the equivalent of hot-working). The new grains, contrary to prediction based on consideration of strain energy at room temperature, tend to be oriented with [0001] parallel to the compression, or normal to the elongation axis.

Moderately strained specimens held for 2 weeks at 450°C in an atmosphere of CO_2 and water (confining pressure 600 atm) show no sign of annealing recrystallization.

Observed resistance of experimentally strained marble to annealing and the minor role of hot-working in our range of experiments contrasts sharply with the prevalence of what seem to be completely recrystallized (annealed) textures in naturally deformed (metamorphic) marbles.

F. J. TURNER, D. T. GRIGGS
University of California

Manipulation of Cerebral Serotonin and Its Relationship to Mental Disorders

In 1954 Woolley and Shaw first produced evidence which suggested that the hormone serotonin played a role in mental processes. The induction of a specific deficiency of serotonin in the brain (by means of antimetabolites of this hormone) led to psychotic episodes in human beings. Since that time considerable additional evidence to support such a view has appeared.

Woolley and Shaw further suggested that the naturally occurring derangements, such as schizophrenia, possibly were due to a lack of serotonin in the brain. This lack could arise from some metabolic failure to produce enough of it in the central nervous system. They demonstrated that such a lack could not be corrected by peripheral administration of serotonin, because such administration did not result in passage of the hormone into the brain in detectable amounts. Consequently the problem arose of how to increase cerebral serotonin by peripheral medication. This has been accomplished by combined use of the special antimetabolite called BAS plus Udenfriend's precursor of serotonin—namely, 5-hydroxytryptophane.

The hydroxytryptophane increases the serotonin in both periphery and brain, and the BAS, which does not readily enter the brain, counteracts the peripheral effects which otherwise are severe. The result is to increase selectively the functioning serotonin content of the brain alone. This has provided a means for direct test of the serotonin-deficiency postulate about the causation of schizophrenia. Preliminary clinical trials on mental patients have suggested that this combined use of BAS and hydroxytryptophane suppresses the disease. Further trials will be needed to establish the point.

D. W. WOOLLEY
Rockefeller Institute for Medical Research

Visualization of Molecular Order in Organic Crystals

It has recently been shown possible [J. W. Menter, *Proc. Roy. Soc.* **236 A**, 119 (1956); L. W. Labaw and R. W. G. Wyckoff, *Proc. Konink. Acad. Amsterdam* **59**, 449 (1956)] to see with the electron microscope what appear to be the molecular separations (of the order of 10 A) in very small and thin crystals of phthalocyanin and its copper and platinum compounds. The visibility of this molecular detail in an organic compound having a molecular weight of no more than about 500 offers many new possibilities for electron microscopy at high resolution.

We have been examining a variety of crystalline organic compounds in the attempt to determine the conditions under which such molecular detail can be seen. Certain of the indanthrene dyes have proved to be favorable objects for this investigation; some of the results thus far obtained with them are described and illustrated

RALPH W. G. WYCKOFF, L. W. LABAW
National Institutes of Health

New Books

Radioactive Isotopes in Agriculture, a Conference. Sponsored by the Council of Participating Institutions of Argonne National Laboratory. U.S. Atomic Energy Commission, Washington, 1956 (order from Supt. of Documents, GPO, Washington 25). 416 pp. $3.

An Introduction to Electrostatic Precipitation in Theory and Practice. H. E. Rose and A. J. Wood. Constable, London, 1956 (order from Essential Books, Fair Lawn, N.J.). 166 pp. $2.80.

Disturbed Communication. The clinical assessment of normal and pathological communicative behavior. Jurgen Ruesch. Norton, New York, 1957. 337 pp. $6.

Osteology of the Reptiles. Alfred S. Romer. University of Chicago Press, Chicago, 1957. 722 pp. $20.

Atoms for the World. United States participation in the Conference on the Peaceful Uses of Atomic Energy. Laura Fermi. University of Chicago Press, Chicago, 1957. 227 pp. $3.75.

In-Service Education for Teachers, Supervisors, and Administrators. Fifty-sixth yearbook, pt. 1. Nelson B. Henry, Ed. National Society for the Study of Education, 1957 (distributed by University of Chicago Press, Chicago, Ill.). 376 pp. Paper, $3.25; cloth, $4.

General Geography for Colleges. O. D. Von Engeln and Bruce C. Netschert. Harper, New York, 1957. 681 pp. $7.50.

Dairy Microbiology. Edwin M. Foster, F. Eugene Nelson, Marvin L. Speck, Raymond N. Doetsch, Joseph C. Olson, Jr. Prentice-Hall, Englewood Cliffs, N.J., 1957. 492 pp. $5.65.

Experimental Psychology and Other Essays. I. P. Pavlov. Philosophical Library, New York, 1957. 653 pp. $7.50.

The Economic Consequences of Automation. Paul Einzig. Norton, New York, 1957. 255 pp. $3.95.

Neoplasms of the Domesticated Mammals, a Review. Review Series No. 4 of the Commonwealth Bureau of Animal Health. E. Cotchin. Commonwealth Agricultural Bureaux, Farnham Royal, Bucks, England, 1956. 100 pp.

Research Project for the Study and Treatment of Persons Convicted of Crimes Involving Sexual Aberrations, Final Report. June 1952 to June 1955. Bernard C. Glueck, Jr., Director. University of Minnesota Medical School, Minneapolis, 1956. 401 pp.

Philosophy of Science. The link between science and philosophy. Philipp Frank. Prentice-Hall, Englewood Cliffs, N.J., 1957. 394 pp. $7.65.

Flotation. A. M. Gaudin. McGraw-Hill, New York, ed. 2, 1957. 573 pp. $12.50.

The Road to Inner Freedom. Baruch Spinoza. Introduction by Dagobert D. Runes, Ed. Philosophical Library, New York, 1957. 215 pp. $3.

Vitamin B_{12} and Intrinsic Factor. H. C. Heinrich, Ed. Enke, Stuttgart, Germany, 1957. 576 pp.

Vergleichende Physiologie. vol. III, *Ernahrung, Wasserhaushalt und Mineralhaushalt der Tiere.* W. von Buddenbrock. Birkhauser, Basel, Switzerland, 1956. 677 pp. DM. 66.

Handbuch der Physik. vol. XX, *Electrical Conductivity II*; 491 pp.; DM. 112. vol. XXX, *X-rays*; 384 pp.; DM. 88. S. Flugge, Ed. Springer, Berlin, 1957.

Chemical Engineering Reports. How to search the literature and prepare a report. Kenneth A. Kobe. Interscience, New York, ed. 4, 1957. 175 pp. $3.

Meetings and Societies

Laboratory Animals

The world demand for laboratory animals continues to increase enormously, especially for uniform high quality and specialized strains. Unless proper steps are taken, it is certain that vital progress in experimental biology and medicine will be delayed or hindered. In addition to numerous national problems of laboratory animal supply and use, there are many of a universal nature which could best be solved on a coordinated international basis.

Consultants on laboratory animals who were convened by UNESCO on 3–4 Dec. 1956 in Paris recommended formation of an International Committee on Laboratory Animals. This committee was established under the auspices of the International Union of Biological Sciences (IUBS), UNESCO, and the Council for International Organizations of Medical Sciences (CIOMS), which includes the International Union of Physiological Sciences, the International Union of Biochemistry, and the International Union against Cancer.

This committee was formed from a reorganization of an IUBS Committee on Laboratory Animals, established in Rome, Italy, in April 1956, and from a program established by UNESCO that was based on recommendations of the Cell Biology Program of CIOMS, of December 1955.

The International Committee on Laboratory Animals consists of (i) a representative of IUBS: Sven O. Hörstadius, president of IUBS, chairman of the committee; (ii) W. Lane-Petter, director, Laboratory Animals Bureau, Medical Research Council, United Kingdom, honorary executive secretary of the committee; (iii) M. M. Sabourdy, director, Centre de Selection des Animaux de Laboratoire, Centre National de la Recherche Scientifique, France; (iv) Dale W. Jenkins, chairman, Institute of Laboratory Animal Resources, National Academy of Sciences–National Research Council, United States; (v) a representative of CIOMS; and (vi) a representative of UNESCO.

The committee is presently surveying the laboratory animal sources and utilization in the United Kingdom and the Benelux countries and in France, Italy, and Scandinavia, including Finland and Iceland. Additional countries will be surveyed in the near future. The committee is patterning its activities, on an international scale, after the programs of the Institute of Laboratory Animal Resources of the National Academy of Sciences–National Research Council (U.S.) and the Laboratory Animals Bureau of the Medical Research Council (U.K.) It is attempting to stimulate formation of similar organizations in other countries.

The aims of this international committee are to ensure adequate supplies of uniformly high-quality laboratory animals and to investigate and determine what action is required to prevent serious shortages from arising. In order to improve the supply and quality of laboratory animals, an international survey is being made of (i) the sources of supply, the numbers, and the kinds of laboratory animals that are produced or procured, and (ii) the main users, the numbers and kinds of laboratory animals that are utilized, and the purposes for which they are used. A world list of strains of laboratory animals is being compiled, and a documentation center will be established. The common terms used in relation to laboratory animals are being defined precisely and quantitatively—terms used with respect to genetics, disease and parasitism, nutrition, care, and performance records (for example, *strain, inbred, pathogen free*). These defined terms will be standardized on an international basis.

The major problems that arise in connection with laboratory animals, such as problems of supply, genetics, disease, nutrition, care, and transportation, are being studied. The requirements for international or local production centers for breeding and supplying inbred and other needed strains of laboratory animals (for example, cancer-susceptible mice) will be determined. A survey is being made of establishments and facilities that could undertake these functions if the need should arise.

The committee will prepare a report on the customs, quarantine, and other regulations concerning international shipment of laboratory animals and will formulate recommendations for proper conditions of transportation.

The committee will also determine the need for establishing an information exchange, an educational program for animal technicians and caretakers, internationally recognized standards for laboratory animals, and systems for certifying animals and accrediting suppliers. It will later examine the possibility of arranging stimulating symposia.

DALE W. JENKINS
National Research Council, Washington, D.C.

Biophysical Conference and Society

A 3-day National Biophysical Conference was held 4–6 Mar. in Columbus, Ohio, to bring together, for scientific communication, those concerned with the whole range of biophysical interest, from macromolecules to the mind of man.

Physicists and biologists contributed 211 papers, on physical aspects of problems bordering on physical chemistry, macromolecular structure, high-polymer chemistry, electrochemistry, protein chemistry, genetics, virology, cellular structure, physiology at several levels of organization, psychophysics, and extrasensory perception and communication theory. The hypothesis was amply verified that most of the 500 or more biophysicists present, from 200 institutions, would find a large proportion of the papers, over such a range, both intelligible and interesting.

The conference was organized in four parallel sessions, preceded each morning and afternoon by plenary meetings that proved to be the highlights of the occasion. Notable 30-minute papers were presented: A. Rich, "Collagen"; S. Benzer, "Genetic structure"; K. S. Cole, "Electrical structure and function of cells"; R. E. Zirkle, "Irradiation in mitosis"; H. K. Hartline, "Neural interactions of the eye"; H. E. v. Giercke, "Vibratory transmission in humans"; C. W. Sheppard, "Theory of mixing"; O. H. Schmitt, "Physics of EKG"; J. D. Hardy, "Thermal stimuli"; and W. A. Rosenblith, "Sensory communication." A round table on "Training and careers," conducted by E. C. Pollard, F. O. Schmitt, M. A. Lauffer, F. D. Carlson, and R. W. Stacy, was of special value. The response to these diverse sessions further attested to the common interests of those present.

The evenings were spent in discussion

of problems of biophysical organization: the purposes, tasks, and forms of scientific relationships pertaining to this field. Since this conference arose from action taken in January 1956, and since many of the issues had been well discussed in meetings prior to and subsequent to that date, it was soon apparent that we had here a "supersaturated solution," which, on 5 March, by nearly unanimous vote, formed a new society. This was named, provisionally, the Biophysical Society. Those present took the steps needed to set up a legal organization and elected, as officers, R. C. Williams, chairman; O. H. Schmitt, vice chairman; R. W. Stacy, treasurer; and S. A. Talbot, secretary. The other members of the first year's council are E. C. Pollard, W. A. Rosenblith, F. D. Carlson, K. S. Cole, H. K. Hartline, M. A. Lauffer, C. Levinthal, E. Rabinowitch, N. R. Rashevsky, A. Rich, R. B. Roberts, F. O. Schmitt, A. K. Solomon, H. B. Steinbach, C. A. Tobias, and R. E. Zirkle.

The purpose of this society is to encourage biophysical research by increasing communication among all those working in this field, by furthering the training of biophysicists, and by upholding standards in the physical analysis of biological problems. Because the physical aspects of biological problems are studied by scientists who are primarily physicists, biologists, or both, the Biophysical Society expects to benefit from including both in its membership. Mathematical, theoretical, experimental, and instrumental aspects are equally a part of this philosophy. It is planned to hold annual meetings, with due regard to the schedules of existing physical and biological societies. The cooperation and representation of the major scientific groups and interests involved were an outstanding feature of the meeting, and affiliations should be in order. Constitutional details and the question of a journal are under consideration.

Local arrangements for the conference, held in the Deshler-Hilton hotel, were made and carried out by R. W. Stacy and members of the biophysics division of Ohio State University. A publicity committee, headed by H. P. Schwan of Pennsylvania, also prepared the printed abstracts. Representative biophysicists from 40 institutions gave assistance in formulating the program and organizational policies to a planning committee composed of K. S. Cole, E. C. Pollard, O. H. Schmitt, and S. A. Talbot.

The nationally representative character of this scientific meeting and the richness of its program were, in large measure, the result of the strong encouragement and support of the U.S. Air Force Office of Scientific Research, which is concerned with many aspects of this field of science. A volume of selected papers from the conference, to be published by the Yale University Press, will show the scope and character of the National Biophysical Conference of 1957.

S. A. TALBOT

Johns Hopkins University

ACS Divison of Inorganic Chemistry

The new division of inorganic chemistry of the American Chemical Society is seeking more members among the many scientists both in and outside the United States who are interested in inorganic chemistry. The membership dues of $3 per year may be sent to Dr. L. B. Asprey, Los Alamos Scientific Laboratory, Box 1663, Los Alamos, N.M. John C. Bailar, Jr., of the University of Illinois, was appointed chairman of the division and John F. Gall, of the Pennsylvania Salt Manufacturing Company, was appointed chairman-elect by the president of ACS after the society's council unanimously approved the formation of the new division with the usual probationary period of not more than 3 years as fixed by the society's bylaws.

Liquid Scintillation Counting

Northwestern University will hold a conference on liquid scintillation counting at the Technological Institute, Evanston, Ill., 20–22 Aug. A wide range of topics on the theory and application of liquid scintillators will be covered by invited papers: coincidence counters, single channel counters, chemistry of liquid scintillators, and applications in biology and medicine, industry, archeology, physics, chemistry, and engineering. Abstracts of nonsolicited papers should be sent to the program chairman, Dr. F. Newton Hayes, Los Alamos, New Mexico, *by 1 June.*

Psychiatric Association

The American Psychiatric Association will hold its 113th annual meeting at the Hotel Morrison, Chicago, Ill., 13–17 May. About 4000 psychiatrists and guests are expected. Francis J. Braceland, APA's president and psychiatrist-in-chief, Institute of Living, Hartford, Conn., will call the meeting to order and deliver the presidential address on the morning of the first day.

Beginning that afternoon, more than 130 scientific papers will be presented. Many scientific exhibits, films, symposia, and other special features are scheduled.

Industrial Nuclear Technology

The second Industrial Nuclear Technology Conference, cosponsored by Armour Research Foundation of Illinois Institute of Technology, and *Nucleonics Magazine,* will be held in the Chicago Museum of Science and Industry, Chicago, Ill., 14–16 May. The purpose of the conference is to provide a platform for scientific interchange on the nonpower aspects of nuclear technology.

A session designed specifically for industrial executives will be held on 14 May. The session will serve to acquaint industrialists with what radiation is and how to use it in industry, where to get nuclear material and what staff is required to handle it, when the Government requires licensing and how the legal matters are handled, and how many dollars will be involved and what sort of equipment is necessary.

The technical sessions will be devoted to an exchange of ideas by scientists on new radiation effects in the solid state and the liquid state for both organic and inorganic materials, nuclear machines and instrumentation, and industrial applications of nuclear radiation and nuclear techniques ranging from measurements on plastic laminates and metal plating efficiency to empirical formula analysis of organic compounds.

A review of nuclear industry in foreign countries will be presented in a panel discussion by foreign physicists during a luncheon on 15 May. Further information may be obttained by writing to the conference cochairman, Leonard Reiffel, Armour Research Foundation of Illinois Institute of Technology, Chicago 16, Ill.

Editorial Conference Formed

Some 50 people interested in the problems of editing biological publications met in New Orleans, La., from 1 to 4 April under the auspices of the American Institute of Biological Sciences and with the financial support of the National Science Foundation. The group decided that the exchange of information and the discussion of common editorial problems should be continued. To further this end, the participants organized a Conference of Biological Editors and adopted a tentative constitution that calls for annual meetings and states that the object of the organization "is to provide an efficient means for cooperation among editors and for furthering effective publication of continuing publications in the fields of biological sciences —serials, reviews, and adjunct media (e.g., microforms)." Membership in the conference is "open to persons who hold

or have held a principal official responsibility for the editorial management" of publications of the kind heretofore mentioned.

The following were elected as the first officers of the conference (terms in parentheses): chairman, Bentley Glass *Quarterly Review of Biology* (2 years); vice chairman, Donald P. Costello, *Biological Bulletin* (2 years); executive secretary, Fred R. Cagle, *Copeia* (3 years). Members-at-large of the Executive Committee are Harold Cummins, *American Journal of Anatomy*; William C. Steere, *American Journal of Botany*; and P. W. Wilson, *Bacteriological Reviews* (terms of from 1 to 3 years to provide for staggering of appointments; individual terms not yet decided).

International Switching Symposium

The International Symposium on the Theory of Switching, sponsored by the Computation Laboratory of Harvard University, took place 2–5 Apr. Switching is central to all binary devices, such as those used in data processing, automatic control, and telephone exchanges. It concerns the mathematical theory of two-state circuits—low-high, off-on, positive-negative, and so forth.

Nearly 1000 scientists and engineers from 14 nations attended. The symposium was made possible by the support of Bell Telephone Laboratories, Inc., International Business Machines Corporation, Radio Corporation of America, and Sperry Rand Corporation. The program was planned and organized by Howard H. Aiken, director of the Computation Laboratory. Spread of interest in large-scale computing machines and similar devices from the United States to all parts of the world was underlined by the many nations represented in the gathering.

Society Elections

■ Animal Care Panel: pres., Jules Cass, University of Cincinnati; 1st v. pres., Bennett J. Cohen, University of California; 2nd v. pres., Victor Schwentker, the West Foundation; sec.-treas., Robert J. Flynn, Argonne National Laboratories.

■ Wildlife Society: pres., A. Starker Leopold, University of California; v. pres., Richard B. Miller, University of Alberta; past-pres., D. L. Allen, Purdue University; exec.-sec., Daniel L. Leedy, U.S. Fish and Wildlife Service.

■ Kappa Delta Pi: pres., Katherine Vickery, Alabama College; 1st v. pres., John J. Harton, Fresno State College; 2nd v. pres., Gerald Read, Kent State University; sec.-treas., E. I. F. Williams, 238 East Perry St., Tiffin, Ohio. Representative to the AAAS Council is Katherine Vickery.

Forthcoming Events

May

13–15. Radiation Research Soc., annual, Rochester, N.Y. (A. Adelmann, Nuclear Science and Engineering Corp., P.O. Box 10901, Pittsburgh 36, Pa.)

13–15. Recent Developments in Research Methods and Instrumentation, symp., Bethesda, Md. (J. A. Shannon, National Institutes of Health, Bethesda.)

13–15. Structure of Electrolytic Solutions, NSF symp., Washington, D.C. (H. B. Linford, Electrochemical Soc., 216 W. 102 St., New York 25.)

13–16. American Orthodontic Assoc., New Orleans, La. (S. D. Goal, 1037 Maison Blanche Bldg., New Orleans.)

13–16. Semiconductor Symposium, 5th annual, Washington, D.C. (H. M. Pollack, Semiconductor Div., RCA, 415 S. 5 St., Harrison, N.J.)

13–17. American Psychiatric Assoc. annual, Chicago, Ill. (D. Blain, APA, 1785 Massachusetts Ave., NW, Washington 6.)

13–17. Inter-American Symposium on the Peaceful Uses of Nuclear Energy, Brookhaven, L.I., N.Y. (S. Tucker, Brookhaven National Lab., Brookhaven, L.I.)

14–16. Industrial Nuclear Technology Conf., Chicago, Ill. (L. Reiffel, Armour Research Foundation, Illinois Inst. of Technology, 10 West 35 St., Chicago 16.)

14–16. International Soc. of Audiology, cong., St. Louis, Mo. (S. R. Silverman, 818 S. Kingshighway, St. Louis 10.)

14–18. Biochemistry of Cancer, symp. of International Union against Cancer, London, England. (E. Boyland, Chester Beatty Research Inst., Royal Cancer Hospital, Fulham Rd., London, S.W.3.)

15–16. Space Age Symposium, Southern Research Inst., Birmingham, Ala. (R. D. Osgood, Jr., Southern Research Inst., 917 S. 20 St., Birmingham 5.)

15–18. American College of Cardiology, Washington, D.C. (S. Fiske, 150 E. 71 St., New York 21.)

15–18. Work and the Heart Medical Conf., Milwaukee, Wis. (E. L. Belknap, Dept. of Occupational and Environmental Medicine, Marquette School of Medicine, Milwaukee.)

16–17. Space Age Symp., Southern Research Inst., Birmingham, Ala. (R. D. Osgood, Jr., Southern Research Inst., 2000 Ninth Ave. South, Birmingham 5.)

16–18. Engineering Industries Exposition, New York, N.Y. (H. Becher, New York State Soc. of Professional Engineers, 1941 Grand Central Terminal Bldg., New York 17.)

16–18. Society of Naval Architects and Marine Engineers, spring, Long Beach, Calif. (W. N. Landers, SNAME, 74 Trinity Pl., New York 6.)

17. Maryland Acad. of Sciences, annual, Baltimore, Md. (T. King, Maryland Acad. of Sciences, Enoch Pratt Free Library Bldg., Baltimore 1.)

17–19. American Inst. of Industrial Engineers, 8th annual, New York, N.Y. (J. L. Southern, AIIE, 145 N. High St., Room 303, Columbus 15, Ohio.)

19–21. Heat Transfer and Fluid Mechanics Inst., Pasadena, Calif. (P. P. Wegener, Jet Propulsion Lab., California Inst. of Technology, 4800 Oak Grove Dr., Pasadena 3.)

19–23. American Assoc. of Cereal Chemists, annual, San Francisco, Calif. (C. L. Brooke, Merck & Co., Inc., Rahway, N.J.)

19–24. National Conf. on Social Welfare, annual, Philadelphia, Pa. (F. Schmidt, NCSW, 22 W. Gay St., Columbus 15, Ohio.)

20–21. Society of American Military Engineers, annual, Washington, D.C. (National Headquarters, SAME, 808 Mills Bldg., Washington 6.)

20–22. Design Engineering Conf., ASME, New York, N.Y. (ASME, 29 W. 39 St., New York 18.)

20–22. International Voice Conf., Chicago, Ill. (H. Von Leden, 30 N. Michigan Ave., Chicago 2.)

20–24. Correctional Psychiatry and Group Counseling, joint institute, Poughkeepsie, N.Y. (P. H. Hoch, Commissioner of Mental Hygiene, State Office Bldg., Albany, N.Y.)

20–24. Mass Spectrometry, New York, N.Y. (R. A. Friedel, U.S. Bureau of Mines, 4800 Forbes St., Pittsburgh 13, Pa.)

20–25. International Conf. of Epizootics, annual, Paris, France. (12, rue de Prony, Paris 17e.)

20–31. International Federation of Agricultural Producers, 9th general assembly, Lafayette, Ind. (IFAP, 712 Jackson Pl., NW, Washington, D.C.)

21–25. American Assoc. on Mental Deficiency, Hartford, Conn. (T. L. McCulloch, Letchworth Village, Thiells, N.Y.)

22–24. American Inst. of Chemists, annual, Akron, Ohio. (L. Van Doren, AIC, 60 E. 42 St., New York 17.)

22–24. American Soc. for Quality Control, annual, Detroit, Mich. (L. S. Eichelberger, A. O. Smith Corp., Milwaukee 1, Wisc.)

22–25. International Scientific Radio Union, national spring mtg., Washington, D.C. (J. P. Hagen, U.S.A. National Committee URSI, National Acad. of Sciences, 2101 Constitution Ave., NW, Washington 25.)

23–25. Acoustical Soc. of America, New York, N.Y. (W. Waterfall, ASA, 57 E. 55 St., New York 22.)

25–26. International Cong. for the Study of the Bronchi, Lisbon, Portugal. (F. Lopo de Carvalho, 138 rua de Junqueira, Lisbon.)

25–28. International Cong. of Acupuncture, 9th, Vienna, Austria. (Austrian Assoc. for Acupuncture, 57 Schwenderstrasse, Vienna.)

26–30. Special Libraries Assoc., annual, Boston, Mass. (Miss M. E. Lucius, SLA, 31 E. 10 St., New York 3.)

29–2. American College of Chest Physicians, annual, New York, N.Y. (M. Kornfeld, ACCP, 112 E. Chestnut St., Chicago 11, Ill.)

30–31. Rheology of Elastomers, conf., Welwyn Garden City, Herts., England. (N. Wookey, British Soc. of Rheology, 52, Tavistock Rd., Edgware, Middlesex, England.)

30–1. American Acad. of Dental Medicine, 11th annual, Boston, Mass. (R. Diamond, 100 Boylston St., Boston.)

30–1. American Malacological Union, Pacific meeting, Santa Barbara, Calif. (Miss M. C. Teskey, P.O. Box 238, Marinette, Wis.)

30–1. Endocrine Soc., 39th annual, New York, N.Y. (H. H. Turner, 1200 N. Walker St., Oklahoma City 3, Okla.)

31–2. American Soc. for the Study of Sterility, New York, N.Y. (H. Thomas, 920 S. 19 St., Birmingham 5, Ala.)

31–2. Social Medicine, internatl. cong., Vienna, Austria. (T. Antoine, Spitalgasse 23, Vienna 9.)

31–2. Society for Applied Anthropology, annual, East Lansing, Mich. (W. F. Whyte, New York State School of Industrial and Labor Relations, Cornell Univ., Ithaca, N.Y.)

June

1–2. American Diabetes Assoc., 17th annual, New York, N.Y. (ADA, 1 E. 45 St., New York 17.)

1–2. Soc. for Investigative Dermatology, annual, New York, N.Y. (H. Beerman, 255 S. 17 St., Philadelphia 3, Pa.)

2–6. Air Pollution Control Assoc., golden anniversary, St. Louis, Mo. Jointly with American Meteorological Soc., American Soc. of Heating and Air Conditioning Engineers, American Inst. of Chemical Engineers, and American Soc. of Mechanical Engineers. (H. C. Ballman, APCA, 4400 Fifth Ave., Pittsburgh 13.)

2–7. Society of Automotive Engineers, summer, Atlantic City, N.J. (Meetings Division, SAE, 29 West 39 St., New York 18.)

2–8. International Cong. of Photobiology, 2nd, Turin, Italy. (G. Matli, Istituto di Fisica dell'Universita di Torino, Via Pietro Giuria 1, Corso Massimo d'Azeglio 46, Turin.)

3–5. American Soc. of Refrigerating Engineers, Miami Beach, Fla. (R. C. Cross, ASRE, 234 Fifth Ave., New York 1.)

3–5. Chemical Inst. of Canada, 40th annual, Vancouver, B.C. (CIC, 18 Rideau St., Ottawa 2, Ont.)

3–7. American Medical Assoc., annual, New York, N.Y. (G. F. Lull, AMA, 535 N. Dearborn St., Chicago 10, Ill.)

3–7. American Soc. of Civil Engineers, Buffalo, N.Y. (W. H. Wisely, ASCE, 33 W. 39 St., New York 18.)

3–7. Hospital Cong., 10th international, Lisbon, Portugal. (J. E. Stone, 10 Old Jewry, London, E.C.2, England.)

3–8. Microbiological Inst., 10th annual, Lafayette, Ind. (C. L. Porter, Dept. of Biological Sciences, Purdue Univ., Lafayette.)

3–12. Quantitative Biology, 22nd Cold Spring Harbor Symp., Cold Spring Harbor, N.Y. (B. Wallace, Biological Laboratory, Cold Spring Harbor.)

4–9. Blood Circulation, international symp., London, England. (D. G. James, c/o 11 Chandos St., London, W.1.)

5–7. Therapeutics, 5th international cong., Utrecht, Netherlands. (F. A. Nelemens, Bureau Provisoire, Vondellaan 6, Utrecht.)

6–7. Production Techniques, 1st natl. symp., IRE, Washington, D.C. (A. A. Lawson, Melpar, Inc., 3000 Arlington Blvd., Falls Church, Va.)

6–8. National Soc. of Professional Engineers, Dallas, Tex. (P. H. Robbins, NSPE, 2029 K St., NW, Washington 6.)

8–11. American Planning and Civic Assoc., annual, Little Rock, Ark. (Miss H. James, APCA, 901 Union Trust Bldg., Washington 5.)

9–12. American Inst. of Chemical Engineers, Seattle, Wash. (F. J. Van Antwerpen, AIChE, 25 W. 45 St., New York 36.)

9–13. American Rocket Soc., semiannual, San Francisco, Calif. (J. J. Harford, ARS, 500 Fifth Ave., New York 36.)

9–13. American Soc. of Mechanical Engineers, semiannual, San Francisco, Calif. (C. E. Davies, ASME, 29 W. 39 St., New York 18.)

10–12. American Nuclear Soc., 3rd annual, Pittsburgh, Pa. (W. W. Grigorieff, ANS, P.O. Box 963, Oak Ridge, Tenn.)

10–12. Canadian Soc. of Microbiologists, annual, London, Ont., Canada. (J. A. Carpenter, Dept. of Bacteriology, Ontario Agricultural College, Guelph.)

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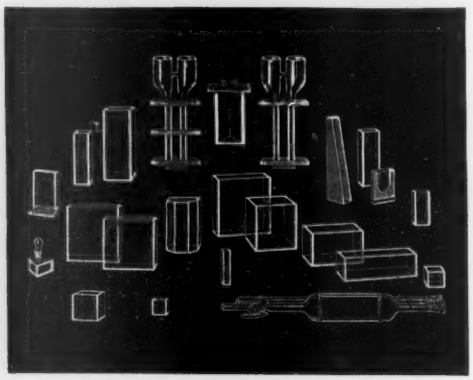

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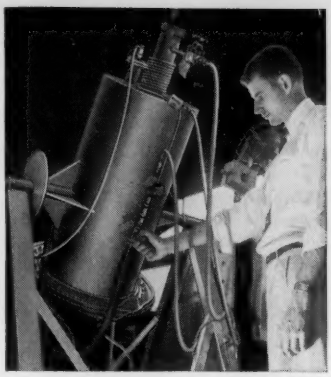

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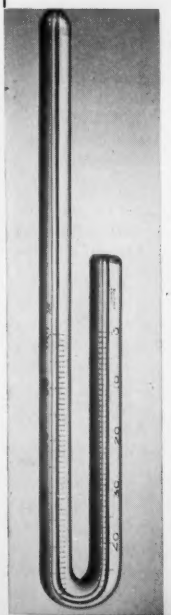

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10–14. Technical Writers' Institute, 5th annual, Troy, N. Y. (J. R. Gould, TWI, Rensselaer Polytechnic Inst., Troy.)

11–13. American Meteorological Soc., Monterey, Calif. (K. C. Spengler, AMS, 3 Joy St., Boston 8, Mass.)

11–15. Ionization Phenomena in Gases, 3rd internatl. conf., Venice, Italy. (U. Facchini, Laboratori CISE, Via Procaccini 1, Milan, Italy.)

12–15. Colloquium of College Physicists, 19th annual, Iowa City, Iowa. (J. A. Van Allen, Dept. of Physics, State Univ. of Iowa, Iowa City.)

16–20. American Soc. of Mammalogists, annual, Lawrence, Kansas. (B. P. Glass, Dept. of Zoology, Oklahoma A.&M. College, Stillwater.)

16–21. American Soc. for Testing Materials, Atlantic City, N.J. (R. J. Painter, ASTM, 1916 Race St., Philadelphia 3, Pa.)

17–19. American Neurological Assoc., Atlantic City, N.J. (C. Rupp, 133 S. 36 St., Philadelphia 4, Pa.)

17–19. Astronomical Soc. of the Pacific, annual, Flagstaff, Ariz. (S. Einarsson, Univ. of California, Berkeley 4.)

17–19. Health Physics Soc., 3rd annual, Pittsburgh, Pa. (H. W. Patterson, Radiation Lab., Univ. of California, Berkeley.)

17–19. Military Electronics, national convention, Washington, D.C. (G. Rappaport, Emerson Radio & Phonograph Corp., 701 Lamont St., NW, Washington 10.)

17–20. Carbon Conf., 3rd, Buffalo, N.Y. (Carbon Conf., Univ. of Buffalo, Buffalo.)

17–20. Institute of Aeronautical Sciences, natl. summer, Los Angeles, Calif. (S. P. Johnston, IAS, 2 E. 64 St., New York 21.)

17–21. American Soc. for Engineering Education, annual, Ithaca, N.Y. (W. L. Collins, Univ. of Illinois, Urbana.)

17–21. Association of Official Seed Analysts, annual, Baton Rouge, La. (L. C. Shenberger, Seed Lab., Dept. of Agricultural Chemistry, Purdue Univ., Lafayette, Ind.)

17–21. Canadian Medical Assoc., 90th annual, Edmonton, Alberta, Canada. (CMA, 244 George St., Toronto, Ont., Canada.)

17–22. Coordination of Galactic Research, internatl. symp., Stockholm, Sweden. (P. T. Oosterhoff, University Observatory, Leiden, Netherlands.)

17–22. Internal Combustion Engine Cong., 4th internatl., Zurich, Switzerland. (C. C. M. Logan, British National Committee, 6 Grafton St., London, W.1.)

17–28. Wear Theory in Metal Cutting and Bearing Design, special summer program, Cambridge, Mass. (Massachusetts Inst. of Technology, Cambridge 39.)

19–21. Association for Computing Machinery, annual, Houston, Tex. (J. Moshman, ACM, 2 E. 63 St., New York 21.)

19–21. Max Planck Soc. for the Advancement of Science, annual general assembly, Lübeck, Germany. (Max Planck Soc. for the Advancement of Science, Kaiserwertherstrasse 164, Dusseldorf, Germany.)

EQUIPMENT NEWS

The information reported here is obtained from manufacturers and from other sources considered to be reliable. Science *does not assume responsibility for the accuracy of the information. All inquiries concerning items listed should be addressed to* Science, *Room 740, 11 W. 42 St., New York 36, N.Y. Include the name(s) of the manufacturer(s) and the department number(s).*

■ ULTRAVIOLET ANALYZER is designed for continuous monitoring and control of petroleum and allied processes. The instrument is of the nondispersive type; filters sensitize it to the component of interest. Radiation wavelengths from 200 to 280 mμ are used. A hydrogen-discharge lamp is the source of illumination. The chopper- and sample-modulated beam is detected by a multiplier phototube. An automatic zero-drift standardization system compensates periodically for long-time drift caused by such factors as fogged windows and lenses, variations in ambient temperature, and aging of the light source. The sample must be clean, dry gas with a flow rate of approximately 1000 cm^3/min. (Consolidated Electrodynamics Corp., Dept. S232)

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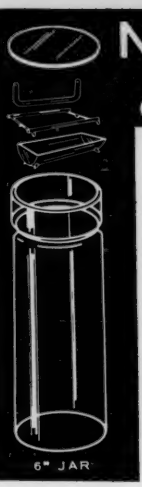

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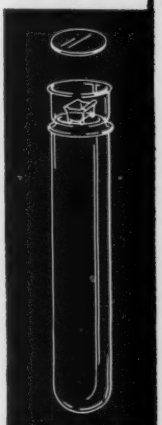

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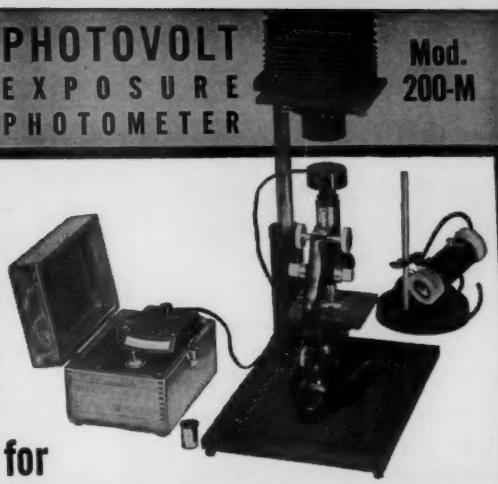

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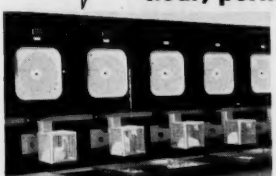

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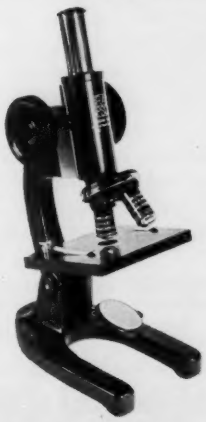

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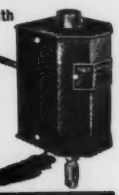

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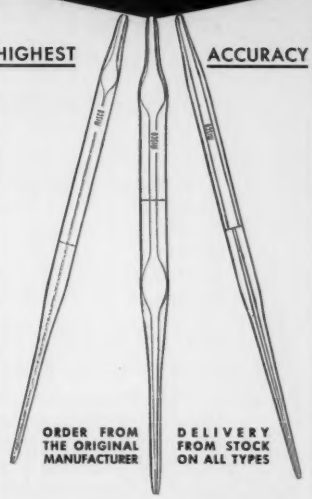

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WATER FOR INDUSTRY

Edited by Jack B. Graham, Leggette, Brashears & Graham, New York, and Meredith F. Burrill, U.S. Department of the Interior.

6 x 9 inches, 141 pages, 18 figures, index, clothbound, 1956.

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No. 45 in the symposium volume series of the American Association for the Advancement of Science.

Industrial productivity requires material resources and human ingenuity, and, of all the material resources, water is used in greater amounts than any other. It constitutes in bulk by far the major constituent of all material commodities required by industry. Sensing the serious nature of the water problem in the coming years, and its pertinence not only to national security but also to internal economic stability, the AAAS invited a panel of experts to present a symposium on *Water for Industry*. It was arranged by the AAAS Section on Geology and Geography, and cosponsored by the Sections on Engineering, Industrial Science, the Geological Society of America, the Association of American Geographers (New England Division), and the American Geophysical Union.

The eventual solution to the problem of water for industry will not involve industry alone, for water is a common property which properly serves not one but many users, and the attainment of peak efficiency of water will not be easily or quickly realized; but not to strive for this husbanding of a vital resource would be as damaging to our national well-being as for a person to ignore a wound and slowly bleed to death.

This book provides a perspective of present and impending water problems, and a wide audience—especially government, industry, geology and geography, and conservation groups —will find it valuable reading.

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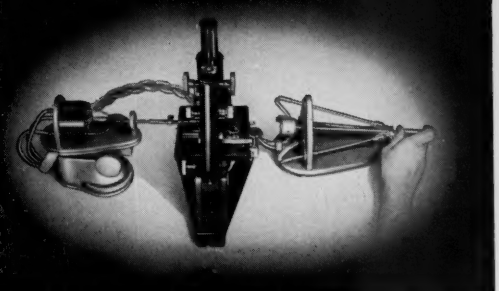

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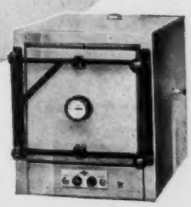

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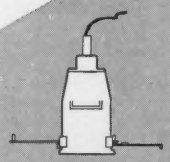

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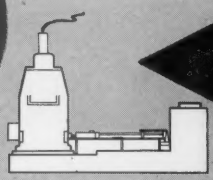

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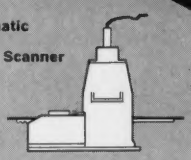

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